

9. Bacterial Infections

Preventative and curative options include:

Vitamin and trace-elements, herbs, lactoferrin, oregano oil, grapefruit seed extract, sarsaparilla root, shark liver oil, bromelain, arginine, cranberry juice, honey, bee propolis, zinc, probiotics, garlic, ionic silver, aloe vera.

Influence of lactoferrin feeding and injection against systemic staphylococcal infections in mice.

Bhimani RS, Vendrov Y, Furmanski P. Department of Biology, New York University, NY, USA.

J Appl Microbiol 1999 Jan;86(1):135-44

Human and bovine lactoferrins (Lfs) and bovine lactoferrin hydrolysate (LH) were assessed in vitro and in vivo for their antibacterial effects on *Staphylococcus aureus*. Lactoferrins showed weak in vitro antibacterial activity while Fe-saturated Lfs and LH showed no activity. Lactoferrin-treated mice (1 mg, i.v.) when injected i.v. with 10(6) staphylococci, showed 30-50% reduction in kidney infections, and viable bacterial counts in the kidneys decreased 5-12-fold. The inhibitory effect was dose-dependent up to 1 mg Lf. Lactoferrins were effective when given 1 day prior to the bacterial challenge, after which there was no significant effect even at doses up to 5 mg. Apo- and Fe-saturated forms of human and bovine Lfs were all equally effective, while LH was not protective. Human and bovine Lfs with different degrees of iron saturation (9-97%) were found to be equipotent. Feeding mice with 2% bLf in drinking water also reduced the kidney infections by 40-60%, and viable bacterial counts, 5-12-fold. The results suggest a potential for the use of Lfs as natural antibacterial proteins for preventing bacterial infections.

Bromelain protects piglets from diarrhoea caused by oral challenge with K88 positive enterotoxigenic *Escherichia coli*.

Chandler DS, Mynott TL. Victorian Institute of Animal Science, Attwood, Australia.

Gut. 1998 Aug;43(2):196-202.

BACKGROUND: K88 positive enterotoxigenic *Escherichia coli* (K88+ ETEC) is an important cause of diarrhoea in young piglets. K88+ ETEC pathogenesis relies on attachment to specific glycoprotein receptors located on the intestinal mucosa. Proteolytic treatment of these receptors in vitro and in vivo prevents attachment of K88+ ETEC to piglet small intestines and may be of clinical use to prevent K88+ ETEC pathogenesis. **AIMS:** To determine whether bromelain, a proteolytic extract obtained from pineapple stems, would protect piglets against K88+ ETEC

diarrhoea and to confirm and extend earlier findings on the effects of bromelain on K88+ ETEC receptors in vivo.

METHODS: Bromelain (0, 12.5, or 125 mg) was orally administered to just weaned piglets for 10 days. One day following commencement of bromelain treatment, piglets were challenged with K88+ ETEC (5 x 10¹⁰ K88ac:0149) for seven days. Intestinal contents from unchallenged piglets were obtained via an intestinal fistula, and tested for their ability to bind K88+ ETEC before and after bromelain treatment.

RESULTS: Both doses of bromelain were successful in reducing the incidence of K88+ ETEC diarrhoea and protected piglets from life threatening disease. Bromelain treated pigs also had significantly increased weight gain compared with untreated pigs. Bromelain only temporarily inhibited K88+ ETEC receptor activity, with receptor activity being regenerated 30 hours following treatment, consistent with the regeneration of new enterocytes.

CONCLUSION: Results show that bromelain can temporarily inactivate ETEC receptors in vivo and protect against ETEC induced diarrhoea. Bromelain may therefore be an effective prophylaxis against ETEC infection.

Antibiotic properties of bovine lactoferrin on *Helicobacter pylori*.

Dial EJ, Hall LR, Serna H, Romero JJ, Fox JG, Lichtenberger LM. Department of Integrative Biology, The University of Texas-Houston Medical School, 77225, USA.

Dig Dis Sci 1998 Dec;43(12):2750-6

To investigate a potential new treatment for gastric *Helicobacter pylori* infection, we have examined the use of the natural antibiotic lactoferrin, found in bovine milk, for activity against *Helicobacter* species both in vitro and in vivo. Lactoferrin was bacteriostatic to *H. pylori* when cultured at concentrations < or =0.5 mg/ml. Growth of *H. pylori* was not inhibited by another milk constituent, lysozyme, or by a metabolite of lactoferrin, lactoferricin B, but growth was inhibited by the iron chelator deferoxamine mesylate. Lactoferrin inhibition of growth could be reversed by addition of excess iron to the medium. Lactoferrin in retail dairy milk was found to be more stable intragastrically than unbuffered, purified lactoferrin. Treatment of *H. felis*-infected mice with lactoferrin partially reversed mucosal disease manifestations. It is concluded that bovine lactoferrin has significant antimicrobial activity against *Helicobacter* species in vitro and in vivo. Bovine lactoferrin should be further investigated for possible use in *H. pylori* infections in man.

New support for a folk remedy: cranberry juice reduces bacteriuria and pyuria in elderly women.

Fleet JC. Human Nutrition Research Center on Aging, Tufts University, Boston, MA 02111.

Cranberry juice has developed a following as a simple, nonpharmacologic means to reduce or treat urinary tract infections, yet the scientific basis for such a claim has been lacking. A new study suggests that bacterial infections (bacteriuria) and associated influx of white blood cells into the urine (pyuria) can be reduced by nearly 50% in elderly women who drink 300 mL of cranberry juice cocktail each day over the course of a 6-month study. The results of this study suggest that consumption of cranberry juice is more effective in treating than preventing bacteriuria and pyuria. Along with earlier reports on the ability of cranberry juice to inhibit bacterial adherence to urinary epithelial cells in cell culture, this new work suggests that drinking cranberry juice each day may be clinically useful. Additional work must be conducted, however, to more completely define the efficacy of cranberry juice.

Human lactoferrin and peptides derived from a surface-exposed helical region reduce experimental *Escherichia coli* urinary tract infection in mice.

Haversen LA, Engberg I, Baltzer L, Dolphin G, Hanson LA, Mattsby-Baltzer I. Departments of Clinical Immunology, Goteborg, Sweden.

Infect Immun 2000 Oct;68(10):5816-23

Lactoferrin (LF) is a multifunctional immunoregulatory protein that has been associated with host defense at mucosal surfaces through its antibacterial properties. The antibacterial and anti-inflammatory properties of LF were further explored with an animal model of experimental urinary tract infection. Bovine LF (bLF), human LF (hLF), and synthetic peptide sequences based on the antibacterial region of hLF (amino acid residues 16 to 40 [HLD1] and 18 to 40 [HLD2]) were given orally to female mice 30 min after the instillation of 10⁸ *Escherichia coli* bacteria into the urinary bladder. The control groups received phosphate-buffered saline or water. C3H/Tif mice were treated with hLF or bLF, and C3H/HeN mice were treated with bLF only. The numbers of bacteria in the kidneys and bladder of C3H/Tif and C3H/HeN mice were significantly reduced 24 h later by the LF treatments compared to the findings for the control group. The hLF-treated group showed the strongest reduction compared with the vehicle-treated-group (P values were 0.009 and 0.0001 for the kidneys and bladder, respectively). The urinary leukocyte response was diminished in the hLF-treated group. The hLF treatment also significantly reduced the urinary interleukin-6 (IL-6) levels at 2 h and the systemic IL-6 levels at 24 h after infection (P values were 0.04 < 0.002, respectively). In the bLF-treated animals, no such strong anti-inflammatory effects were obtained. In another series of experiments, C3H/Tif mice perorally treated with HLD1 or HLD2 also showed reduced numbers of bacteria in the kidneys compared with the vehicle-treated mice, although the results were significantly different only for HLD2 (< 0.01). Analysis of urine from hLF-fed C3H/Tif mice showed that hLF was excreted into the urinary tract at 2 h after feeding. Testing of the *in vitro* bactericidal activity of LF (1 mg/ml) or the peptides (0.1 mg/ml) in mouse urine against the *E. coli* bacteria revealed moderate killing only by HLD2. In conclusion, these results demonstrate for the

first time that oral administration of hLF or peptides thereof is effective in reducing infection and inflammation at a remote site, the urinary tract, possibly through transfer of hLF or its peptides to the site of infection via renal secretion. The antibacterial mechanism is suggested to involve bactericidal capacities of LF, fragments thereof, or its peptides.

Randomised trial of cranberry-lingonberry juice and Lactobacillus GG drink for the prevention of urinary tract infections in women.

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BMJ 2001 Jun 30;322(7302):1571

OBJECTIVE: To determine whether recurrences of urinary tract infection can be prevented with cranberry-lingonberry juice or with Lactobacillus GG drink.
Design: Open, randomised controlled 12 month follow up trial.

SETTING: Health centres for university students and staff of university hospital.

PARTICIPANTS: 150 women with urinary tract infection caused by Escherichia coli randomly allocated into three groups. **Interventions:** 50 ml of cranberry-lingonberry juice concentrate daily for six months or 100 ml of lactobacillus drink five days a week for one year, or no intervention. **Main outcome measure:** First recurrence of symptomatic urinary tract infection, defined as bacterial growth $<=10^5$ colony forming units/ml in a clean voided midstream urine specimen.

RESULTS: The cumulative rate of first recurrence of urinary tract infection during the 12 month follow up differed significantly between the groups ($P=0.048$). At six months, eight (16%) women in the cranberry group, 19 (39%) in the lactobacillus group, and 18 (36%) in the control group had had at least one recurrence. This is a 20% reduction in absolute risk in the cranberry group compared with the control group (95% confidence interval 3% to 36%, $P=0.023$, number needed to treat=5, 95% confidence interval 3 to 34).

CONCLUSION: Regular drinking of cranberry juice but not lactobacillus seems to reduce the recurrence of urinary tract infection.

The gut. A key metabolic organ protected by lactoferrin during experimental systemic inflammation in mice.

Kruzel ML, Harari Y, Chen CY, Castro GA. Department of Integrative Biology, Pharmacology and Physiology, University of Texas Medical School, Houston, USA.

Adv Exp Med Biol 1998;443:167-73

The gastrointestinal tract may be viewed as an ecologic system in which a balance between the host and bacterial flora exists. Two major host components appear to be involved in maintaining this balance. The first is a non-specific structural barrier provided by the epithelial layer of the gastrointestinal mucosae. The second component involves functional immunological elements found in the mucosal and submucosal compartments, e.g., gut associated lymphoid tissue. When gut integrity is disrupted by invasive pathogens or by trauma, a myriad of pro-inflammatory mediators are released from cells in the gut wall that exert actions in the tissue or gut lumen. One of these mediators is lactoferrin, an iron binding protein found in high concentration in most human exocrine secretions. Despite controversies on its physiological role, evidence is emerging that lactoferrin plays an important role in host defense against toxic metabolites and antigenic components of potential pathogens²⁻⁴. This manuscript is intended to provide an overview of work related to lactoferrin's modulatory roles in inflammation, and to present observations from experimental studies on the preservation of intestinal structure and function by lactoferrin during intestinal inflammation. The possibility that lactoferrin limits the autodestructive inflammatory responses presents a new alternative for the future management of systemic inflammation.

Sensitivity of food pathogens to garlic (*Allium sativum*).

Kumar M, Berwal JS. Department of Animal Products Technology, CCS Haryana Agricultural University, Hisar, India.

J Appl Microbiol 1998 Feb;84(2):213-5

The inhibitory activity of garlic (*Allium sativum*) against *Staphylococcus aureus*, *Salmonella typhi*, *Escherichia coli* and *Listeria monocytogenes* was measured by the 'turbidity' method. Minimum inhibitory concentration (MIC) of garlic at 80% inhibition level was calculated for these bacteria. All bacterial pathogenic strains tested were inhibited by garlic; *E. coli* was most sensitive and *Listeria monocytogenes* was least sensitive. Therefore, garlic has potential for the preservation of processed foods.

Direct evidence of the generation in human stomach of an antimicrobial peptide domain (lactoferricin) from ingested lactoferrin.

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Biochim Biophys Acta 1998 Dec 8;1429(1):129-41

The ability to define specific alterations in the structure and function of proteins as they are introduced and processed in vivo remains an important goal. We have evaluated the generation, in vivo, of an antimicrobial peptide (lactoferricin) derived from ingested bovine lactoferrin by surface-enhanced laser desorption/ionization (SELDI). SELDI was used in the affinity mass spectrometry operational mode to detect and quantify lactoferricin directly from unfractionated

gastric contents using a chemically defined ligand with a terminal n-butyl group as the lactoferricin affinity capture device. By this method, we were able to detect and quantify lactoferricin directly upon examination of unfractionated gastric contents recovered from an adult subject 10 min after ingestion of bovine lactoferrin (200 ml of 10 mg/ml (1.2×10^{-4} mol/l) solution). Lactoferricin produced in vivo was directly captured by a surface-enhanced affinity capture (SEAC) device composed of molecules with a terminal n-butyl group and analyzed by laser desorption/ionization time-of-flight mass spectrometry. The recovery of standard lactoferricin or lactoferrin added to an aliquot of the gastric contents was determined to be nearly 100%, confirming the efficiency of this method. The amount of lactoferricin detected in the gastric contents was 16.9 ± 2.7 microg/ml ($5.4 \pm 0.8 \times 10^{-6}$ mol/l). However, a large proportion of ingested lactoferrin was found to be incompletely hydrolyzed. Lactoferrin fragments containing the lactoferricin region were analyzed by in situ pepsin hydrolysis after being captured on the SEAC device. Partially degraded lactoferrin fragments containing the lactoferricin region, including fragments corresponding to positions 17-43, 17-44, 12-44, 9-58 and 16-79 of the bovine lactoferrin sequence, were found to be present at concentrations as high as $5.7 \pm 0.7 \times 10^{-5}$ mol/l. These results suggest that significant amounts of bovine lactoferricin would be produced in the human stomach following ingestion of food, such as infant formula, supplemented with bovine lactoferrin. We propose that physiologically functional quantities of human lactoferricin could be generated in the stomach of breast-fed infants, and possibly, in the case of adults, from lactoferrin secreted into saliva.

The protective effects of lactoferrin feeding against endotoxin lethal shock in germfree piglets.

Lee WJ, Farmer JL, Hilty M, Kim YB. Finch University of Health Sciences/The Chicago Medical School, Illinois 60064, USA.

Infect Immun 1998 Apr;66(4):1421-6

The unique germfree, colostrum-deprived, immunologically "virgin" piglet model was used to evaluate the ability of lactoferrin (LF) to protect against lethal shock induced by intravenously administered endotoxin. Piglets were fed LF or bovine serum albumin (BSA) prior to challenge with intravenous *Escherichia coli* lipopolysaccharide (LPS), and temperature, clinical symptoms, and mortality were tracked for 48 h following LPS administration. Prefeeding with LF resulted in a significant decrease in piglet mortality compared to feeding with BSA (16.7 versus 73.7% mortality, < 0.001). Protection against the LPS challenge by LF was also correlated with both resistance to induction of hypothermia by endotoxin and an overall increase in wellness, as quantified by a toxicity score developed for these studies. In vitro studies using a flow cytometric assay system demonstrated that LPS binding to porcine monocytes was inhibited by LF in a dose-dependent fashion, suggesting that the mechanism of LF action in vivo may be inhibition of LPS binding to monocytes/macrophages and, in turn, prevention of induction of monocyte/macrophage-derived inflammatory-toxic cytokines.

Impedance measurements to study the antimicrobial activity of essential oils from Lamiaceae and Compositae.

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Int J Food Microbiol 2001 Aug 5;67(3):187-95

A wide range of essential oils from sage, mint, hyssop, camomile and oregano were tested for their inhibitory effects against nine strains of gram-negative bacteria and six strains of gram-positive bacteria. Three principles were used in describing the antimicrobial effects of the essential oils: the overall antimicrobial activity determined by use of an impedometric method, the bactericidal effect determined as colony forming units after exposure to the essential oils, and the number of apparent dead cells determined after further enrichment. The data obtained indicate that while the essential oils of sage, mint, hyssop and camomile had generally a bacteriostatic activity, the essential oil from oregano appeared to be bactericidal at concentrations above 400 ppm, probably because of high contents in phenolic compounds. For the other essential oils, the chemical analysis was unable to explain the antimicrobial effect. The bacteriostatic activity was more marked against gram-positive bacteria; in contrast, the bactericidal activity was greatest against gram-negative bacteria. The most sensitive strain was *Escherichia coli* O157:H7 and, of the gram-positive species even at the lowest oil concentrations, *Listeria innocua* was the most sensitive. The data obtained from the study of the bactericidal effect of oregano essential oil indicated that the major part of the species was irreversibly inactivated, i.e. they could not be revived by enrichment.

Immunochemical and physico-chemical characteristics of lactoferrin in human body fluids. [Article in Russian]

Nikolaev AA, Anshakova NI.

Vopr Med Khim 1985 May-Jun;31(3):128-32

It is proved that lactoferrins of different human body fluids (sperm, saliva, milk, tears, urine, bile, sweat, liquor, lymph, blood serum) are immunochemically identical. The lactoferrin is purified from milk, saliva and sperm and the identity of physical and chemical properties of lactoferrins of various origins is proved. The quantitative estimation of the contents of this protein in normal body fluids is given. It is detected the dependence of this protein' electrophoretic mobility and isoelectric point of degree of iron saturation. It is found that lactoferrin is capable to form complexes with esterase.

Antibacterial activity of *Hydrastis canadensis* extract and its major isolated alkaloids.

Scazzocchio F, Cometa MF, Tomassini L, Palmery M. Istituto di Microbiologia, Universita "La Sapienza", Roma, Italia.

Planta Med 2001 Aug;67(6):561-4

The antibacterial activity of extract and isolated major alkaloids (berberine, beta-hydrastine, canadine and canadine) of *Hydrastis canadensis* L. (Ranunculaceae) was evaluated against 6 strains of microorganism: *Staphylococcus aureus* (ATCC 25 993 and ATCC 6538P), *Streptococcus sanguis* (ATCC 10 556), *Escherichia coli* (ATCC 25 922), *Pseudomonas aeruginosa* (ATCC 27 853). Bactericidal activity was evaluated by contact test by measuring the "killing time" on a low density bacterial inoculum, and bacteriostatic activity in liquid medium by M.I.C. values. The results provide a rational basis for the traditional antibacterial use of *Hydrastis canadensis*.

Electron microscopic and microcalorimetric investigations of the possible mechanism of the antibacterial action of a defined propolis provenance.

Takaisi-Kikuni NB, Schilcher H Department de Microbiologie, Faculte de Pharmacie, Universite de Kinshasa, Zaire.

Planta Med. 1994 Jun;60(3):222-7

Microcalorimetric and electron microscopic studies on the mode of the antibacterial action of propolis were performed on *Streptococcus agalactiae*. It was shown that propolis inhibits bacterial growth by preventing cell division, thus resulting in the formation of pseudo-multicellular streptococci. In addition, propolis disorganized the cytoplasm, the cytoplasmic membrane, and the cell wall, caused a partial bacteriolysis, and inhibited protein synthesis. It was evident that the mechanism of action of propolis on bacterial cells is complex and a simple analogy cannot be made to the mode of action of any classic antibiotics.

Antimicrobial peptides of lactoferrin.

Tomita M, Takase M, Wakabayashi H, Bellamy W. Nutritional Science Laboratory, Morinaga Milk Industry Co. Ltd., Kanagawa, Japan.

Adv Exp Med Biol 1994;357:209-18

Lactoferrin was found to contain an antimicrobial sequence near its N-terminus which appears to function by a mechanism distinct from iron chelation. Antimicrobial peptides representing this domain were isolated following pepsin cleavage of human lactoferrin and bovine lactoferrin. The antimicrobial sequence was found to consist mainly of a loop of 18 amino acid residues formed by a disulfide bond between cysteine residues 20 and 37 of human lactoferrin, or 19 and 36 of bovine lactoferrin. The identified domain contains a high proportion of basic residues, like various other antimicrobial peptides known to target microbial membranes and it appears to be located on the surface of the folded protein allowing its interaction with surface components of microbial cells. The isolated domain, "lactoferrin", was shown to have potent broad spectrum antimicrobial properties and its effect was lethal causing a rapid loss of colony-forming capability. Such evidence points to the conclusion that this domain is the

structural region responsible for the microbicidal properties of lactoferrin. The evidence also suggests the possibility that active peptides produced by enzymatic digestion of lactoferrin may contribute to the host defense against microbial disease.

Antimicrobial activity of some commercial extracts of propolis prepared with different solvents.

Tosi B.; Donini A.; Romagnoli C.; Bruni A. Institute of Botany, University of Ferrara, Corso Porta Mare 2,I-44100 Ferrara Italy

Phytotherapy Research (United Kingdom) 1996, 10/4 (335-336)

Some commercial extracts of propolis obtained with different solvents were tested to evaluate their antibacterial and antifungal activity. All propolis preparations exhibited antimicrobial activity, particularly against Gram- positive bacteria, yeasts and dermatophytes with zones of inhibition ranging from 3 to 30 min. Against yeasts and dermatophytes, oil, ethanol and propylene glycol solutions showed an inhibition for more 2 weeks, while the glycerine solution maintained inhibition only for some days. The results indicate that the solvent employed for the extraction may enhance the potency of the antimicrobial activity of propolis. Consistency in the properties and characteristics of propolis were related to the formulation of extraction procedures.

Lactoferricin of bovine origin is more active than lactoferricins of human, murine and caprine origin.

Vorland LH, Ulvatne H, Andersen J, Haukland H, Rekdal O, Svendsen JS, Gutteberg TJ. Department of Medical Microbiology, University Hospital, Tromso, Norway.

Scand J Infect Dis 1998;30(5):513-7

The antimicrobial peptide lactoferricin is generated by gastric pepsin cleavage of lactoferrin. We have examined the antimicrobial activity of lactoferricins derived from lactoferrin of human, murine, caprine and bovine origin with minimal inhibitory concentration (MIC) and minimal bactericidal concentration (MBC) against *E. coli* ATCC 25922 and *S. aureus* ATCC 25923. We found that lactoferricin of bovine origin (Lf-cin B) was the most efficacious of the lactoferricins tested. By comparing the linear and cyclic Lf-cin B we found the cyclic peptide to be the most active. Lactoferricin B was moderately active against *E. coli* ATCC 25922 and *S. aureus* ATCC 25923, but had no activity against *P. mirabilis* or *Y. enterocolitica*. Lf-cin B showed good activity against *C. albicans*, *C. tropicalis* and *C. neoformans*.

Effects of nitric oxide synthase inhibitors on systemic hypotension, cytokines and inducible nitric oxide synthase expression and lung injury following endotoxin administration in rats.

Wang D, Wei J, Hsu K, Jau J, Lieu MW, Chao TJ, Chen HI. Department of Medical Research, Cheng Hsin General Hospital, Taipei, Republic of China.

J Biomed Sci 1999 Jan;6(1):28-35

Endotoxin shock is characterized by systemic hypotension, hyporeactiveness to vasoconstrictors and acute lung edema. A nitric oxide synthase (NOS) inhibitor, NG-monomethyl-L-arginine (L-NMMA) has been shown to be effective in reversing acute lung injury. In the present study, we evaluated the effects of NOS blockade by different mechanisms on the endotoxin-induced changes. In anesthetized rats, lipopolysaccharide (LPS, *Klebsiella pneumoniae*) was administered intravenously in a dose of 10 mg/kg. LPS caused sustained systemic hypotension accompanied by an eightfold increase of exhaled NO during an observation period of 4 h. After the experiment, the lung weight was obtained and lung tissues were taken for the determination of mRNA expressions of inducible NOS (iNOS), interleukin-1beta (IL-1beta) and tumor necrosis factor-alpha (TNF-alpha). Histological examination of the lungs was also performed. In the control group injected with saline solution, mRNA expressions of iNOS, IL-1beta and TNF-alpha were absent. Four hours after LPS, the mRNA expressions of iNOS and IL-1beta were still significantly enhanced, but TNF-alpha was not discernibly expressed. LPS also caused a twofold increase in lung weight. Pathological examination revealed endothelial damage and interstitial edema. Various NOS inhibitors were given 1 h after LPS administration. These agents included Nomega-nitro-L-arginine methyl ester (L-NAME, 10 mg/kg), a constitutive NOS and iNOS inhibitor; S, S'-1,4-phenylene-bis-(1,2-ethanediny) bis-isothiourea dihydrobromide (1,4-PBIT, 10 mg/kg), a relatively specific iNOS inhibitor, and dexamethasone (3 mg/kg), an inhibitor of iNOS expression. These NOS inhibitors all effectively reversed the systemic hypotension, reduced the exhaled NO concentration and prevented acute lung injury. The LPS-induced mRNA expressions of iNOS and IL-1beta were also significantly depressed by these NOS inhibitors. Our results suggest that NO production through the iNOS pathway is responsible for endotoxin-induced lung injury. Certain cytokines such as IL-1beta are possibly involved. These changes are minimized by NOS inhibitors through different mechanisms.

Interspecies coaggregation of plaque bacteria with a cranberry juice constituent.

Weiss EI, Lev-Dor R, Kasham Y, Goldhar J, Sharon N, Ofek I. Department of Oral Biology, Maurice and Gabriela Goldschlager School of Dental Medicine, Tel Aviv University, Israel.

J Am Dent Assoc 1998 Dec;129(12):1719-23

Dental plaque stability depends on bacterial adhesion to acquired pellicle, and on interspecies adhesion (or coaggregation). A high-molecular-weight cranberry constituent at 0.6 to 2.5 milligrams per milliliter reversed the coaggregation of 49 (58 percent) of 84 coaggregating bacterial pairs tested. It acted preferentially on pairs in which one or both members are gram-negative anaerobes frequently

involved in periodontal diseases. Thus, the anticoaggregating cranberry constituent has the potential for altering the subgingival microbiota, resulting in conservative control of gingival and periodontal diseases. However, the high dextrose and fructose content of the commercially available cranberry juice makes it unsuitable for oral hygiene use, and the beneficial effect of the high-molecular-weight constituent requires animal and clinical studies.

Lactoferrin binding by leukemia cell lines.

Yamada Y, Amagasaki T, Jacobsen DW, Green R.

Blood 1987 Jul;70(1):264-70

Monocytes and macrophages have receptors for the iron-binding protein lactoferrin. Lactoferrin acts as a potent inhibitor of granulocyte-macrophage colony stimulating factor production when it binds to these cells. Using a rosette assay and immunofluorescence, we have shown that cultured leukemia cells, including the human erythroid leukemia cell line K562, also have lactoferrin binding sites. The number of binding sites on K562 cells was estimated using soluble ⁵⁹Fe-lactoferrin. Inhibition studies demonstrate that lactoferrin binding sites are distinct and unrelated to receptors for transferrin or the Fc portion of IgG, which are present on K562 cells. However, electrostatic forces may be important for lactoferrin binding, since other polycationic proteins (eg, protamine) inhibit lactoferrin binding. Prior treatment of K562 cells with trypsin nearly abolishes lactoferrin binding. However, these cells recover their ability to bind lactoferrin when trypsin is removed. Unlike transferrin receptors, the expression of lactoferrin binding sites is not regulated by cellular iron status. Cytosine arabinoside arrests the proliferation of K562 cells and simultaneously leads to a reduction in lactoferrin surface binding, suggesting that lactoferrin binding may be dependent on cell proliferation.

Effects of copper and zinc ions on the germicidal properties of two popular pharmaceutical antiseptic agents, cetylpyridinium chloride and povidone-iodine.

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Analyst (United Kingdom), 1998, 123/3 (503-507)

The effects of copper and zinc ions on the rate of killing of Gram-negative bacterium *Pseudomonas aeruginosa*, Gram-positive bacterium *Staphylococcus aureus* and fungal yeast *Candida albicans* by antiseptic agents cetylpyridinium chloride and povidone-iodine (Betadine) were investigated. In the 48 test cases copper and zinc ions clearly potentiated the antiseptic agents in 28 (58.3%) cases and exhibited an improved (not clear potentiation) activity in 15 (31.3%) cases. In five (10.4%) cases there was no change in the antiseptics' antimicrobial activity. In general zinc potentiated the antiseptic agents more than copper. If an 'improved

activity' was the only criterion for this study, then a more rapid antimicrobial effect was observed in 43 out of the 48 test cases, i.e., 90%.

Bromelain prevents secretion caused by *Vibrio cholerae* and *Escherichia coli* enterotoxins in rabbit ileum in vitro

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Gastroenterology (United States) 1997, 113/1 (175-184)

Background and Aims: Diarrhea is a major cause of illness and death in children and young animals. The aim of this study was to investigate the possible therapeutic effect of bromelain, a proteolytic extract obtained from pineapple stems on bacterial toxin and second-messenger agonist-induced intestinal secretion.

Methods: The effect of bromelain pretreatment on short-circuit responses to *Escherichia coli* heat-labile enterotoxin, heat-stable enterotoxin, and *Vibrio cholerae* cholera toxin was evaluated in rabbit ileum mounted in Ussing chambers.

Results: Bromelain was 62% effective in preventing heat-stable enterotoxin-induced secretion, 51% effective against cholera toxin, and 35% effective against heat-labile enterotoxin. Bromelain also prevented secretory changes caused by prostaglandin E₂, theophylline, calcium-ionophore A23187, 8-bromoadenosine 3':5'-cyclic monophosphate, and 8-bromoguanosine 3':5'-cyclic monophosphate, well-known intracellular mediators of ion secretion. The efficacy of bromelain was not caused by reduced tissue viability resulting from its proteolytic effects on enterocytes, indicated by experiments measuring uptakes of nutrients into intestinal cells and experiments measuring short-circuit responses to glucose.

Conclusions: Bromelain prevents intestinal fluid secretion mediated by secretagogues that act via adenosine 3':5'-cyclic monophosphate, guanosine 3':5'-cyclic monophosphate, and calcium-dependent signaling cascades. It may be clinically useful as an antidiarrheal drug.

New support for a folk remedy: Cranberry juice reduces bacteriuria and pyuria in elderly women

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Nutrition Reviews (United States) 1994, 52/5 (168-170)

Cranberry juice has developed a following as a simple, nonpharmacologic means to reduce or treat urinary tract infections, yet the scientific basis for such a claim

has been lacking. A new study suggests that bacterial infections (bacteriuria) and associated influx of white blood cells into the urine (pyuria) can be reduced by nearly 50% in elderly women who drink 300 mL of cranberry juice cocktail each day over the course of a 6-month study. The results of this study suggest that consumption of cranberry juice is more effective in treating than preventing bacteriuria and pyuria. Along with earlier reports on the ability of cranberry juice to inhibit bacterial adherence to urinary epithelial cells in cell culture, this new work suggests that drinking cranberry juice each day may be clinically useful. Additional work must be conducted, however, to more completely define the efficacy of cranberry juice.

Relationship between residual metal ions in a solution and the inhibitory capability of the metal ions for pathogenic bacterial growth

Zhao Z.-H.; Sakagami Y.; Osaka T. Z.-H. Zhao, Satosen Co., Ltd., 2-20-65 Tamadenishi, Nishinari-ku, Osaka 557 Japan

Bulletin of the Chemical Society of Japan (Japan), 1998, 71/4 (939-945)

The inhibitory capability of various low concentrations of six kinds of metal ions [silver(I), copper(II), cobalt(II), nickel(II), zinc(II), and dichromate] for pathogenic bacterial (gram-positive bacteria *Staphylococcus aureus* and MRSA, gram-negative bacteria *Escherichia coli* and *Pseudomonas aeruginosa*) growth was quantitatively determined exactly. Residual metal-ion concentrations in a phosphate buffer solution after being incubated with pathogenic bacteria were then measured by an atomic-absorption spectrophotometer. We found that the inhibitory capability of metal ions correlated with the residual metal concentrations. Based on the biochemical and chemical situation, the mechanisms of the inhibitory capability of the metal ions are discussed. In addition, the determined minimum inhibitory concentration (MIC) values of metal ions on tested bacteria are considered.

Effects of zinc oxide on the attachment of *Staphylococcus aureus* strains

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Journal of Dermatological Science (Ireland), 1998, 17/1 (67-74)

We examined the attachment of *Staphylococcus aureus* to plastic tissue- culture coverslips after incubation for 24 h. The attachment to coverslips was weaker in rabbit plasma with 5% zinc oxide (ZnO) than in the control rabbit plasma without ZnO (< 0.01). Plasma coagulation by *S. aureus* strains was not detected in plasma with 5% ZnO after incubation for 24 h. The membranous structure (an immature biofilm) was formed on the coverslips by *S. aureus* cells in plasma after incubation for 24 h. The colony counts of *S. aureus* cells on the membranous structures were lower in plasma with 5% ZnO, plasma with 0.2% hinokitiol, plasma with 5% ZnO + 0.2% hinokitiol, plasma with cefdinir at 4 minimum

inhibitory concentration (MIC) and plasma with levofloxacin at 4 MIC, than in the control plasma after incubation for 24 h (< 0.01). The colonies on the membranous structures completely disappeared in the case of plasma with 5% ZnO and 0.2% hinokitiol. The colony counts on membranous structures were lower in plasma with cefdinir at 4 MIC or levofloxacin at 4 MIC containing 5% ZnO than in plasma with cefdinir at 4 MIC or levofloxacin at 4 MIC only, (< 0.05). The MICs of hinokitiol against *S. aureus* strains peaked at an MIC distribution of 16-32 microg/ml. The peak shifted to below 1 microg/ml by adding 5% ZnO in agar plate method. The results suggest that the attachment of *S. aureus* cells to the coverslips is suppressed in the presence of 5% ZnO and that antistaphylococcal activities of cefdinir, levofloxacin and hinokitiol increase in the presence of 5% ZnO.

Toxicity of hydrogen peroxide produced by electroplated coatings to pathogenic bacteria

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Canadian Journal of Microbiology (Canada), 1998, 44/5 (441-447)

The ability of various electroplated coatings (cobalt, zinc, copper, and cobalt-containing alloys of nickel, zinc, chromium, etc.) to inhibit the growth of pathogenic bacteria (Gram-positive bacteria *Enterococcus faecalis* and methicillin-resistant *Staphylococcus aureus* and Gram-negative bacteria *Escherichia coli*, *Pseudomonas aeruginosa*, and *Klebsiella pneumoniae*) was determined by a drop-method antibacterial experiment. The amounts of H₂O₂, produced and metal ions dissolved from the surfaces of various electroplated coatings were measured and it was found that the inhibitory ability of coatings corresponded to the amounts of H₂O₂ produced. The more significant the inhibition of the coating to bacterial growth, the greater the amount of H₂O₂ production. In addition, the bacterial survival rates on the surfaces of coatings were almost zero when H₂O₂ was produced in amounts greater than 10⁻⁶ mmol/cm². However, the dominant concentrations of metal ions dissolved from coatings were outside of the bacterial lethal range.

Small bowel bacterial overgrowth syndrome

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Scand. J. Gastroenterol. Suppl. (Norway), 1983, 18/85 (83-93)

Different aspects of the small bowel bacterial overgrowth syndrome are reviewed. Special emphasis is put on the newly recognized structural and functional abnormalities of the small intestinal mucosa, abnormalities that may not be fully reversed by effective antimicrobial therapy. The pathogenetic mechanisms involved in the malabsorption of different substances are discussed and the available diagnostic tests are briefly presented. The current therapy, surgical, medical and supportive, are outlined. It is pointed out that abnormal overgrowth

flora of the small intestine can occur unassociated with malabsorption. Thus, the clinician must assess the potential benefit to be derived from treatment, once the presence of absorptive abnormalities is documented.

Screening of oriental herbal medicines for antibacterial activities

O Sung Bae; Jae Ock Hwang; Duk Kyun Ahn; Woo E.-R.; Seon Hee Seo; Hyung Ja Kim; Park H. E.-R. Woo, Division of Applied Medicine, Korea Inst. of Sci. and Technology, P.O. Box 131, Cheongryang, Seoul 130-650 South Korea

Natural Product Sciences (South Korea), 1998, 4/1 (32-37)

The water extracts of oriental herbal medicines which have been clinically used to treat bacterial infections in Korea were screened for in vitro antibacterial activity by the paper disc assay method. Two Gram positive bacteria, *Staphylococcus aureus* SG511, *Bacillus subtilis* ATCC 6633 and two Gram negative bacteria, *Escherichia coli* 055, *Pseudomonas aeruginosa* 9027 were used as test organisms. Among 83 of the extracts tested, 25 were active against *Staphylococcus aureus* SG 511, 9 were active against *Bacillus subtilis* ATCC 6633, while none showed inhibitory activity against *Escherichia coli* 055 and *Pseudomonas aeruginosa* 9027. Among them, Hwangyonhaedoktang plus hwangyon, Chongwisan, and Ssangbaksan showed remarkably potent antibacterial activity.

Antimicrobial activity of honey on selected microorganisms: A preliminary study

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Biomedical Research (India), 1998, 9/1 (51-54)

This prospective study was undertaken to investigate the in-vitro antimicrobial activity of honey. Two hundred and forty-six bacterial strains of which 233 were multiple-drug resistant clinical isolates and 13 Difco antibiotic susceptibility control strains obtained from the American Type Culture Collection (ATCC) and Center for Disease Control (CDC) cultures were tested against crude unprocessed honey. This type of honey exhibited a fairly good antimicrobial activity against both Gram-negative and Gram-positive bacteria. A remarkable activity was observed with *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Staphylococcus aureus*.

Malnutrition and bacterial infections in hepatic cirrhosis

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GED - Gastreenterologia Endoscopia Digestiva (Brazil), 1997, 16/6 226-230)

Malnutrition is an important factor in the pathogenesis of hepatic diseases and, due to its relation to immunologic alterations, it may lead to the onset of infections. The aim of this study was to prospectively evaluate the nutritional status of 170 hospitalized patients who presented with alcoholic cirrhosis, whether or not associated to bacterial infections. All patients were submitted to biochemical and hepatic blood tests, bacteriological and bacterioscopic analyses, blood and ascitic fluid cultures, Child-Pugh classification, and nutritional evaluation through subjective and objective analyses using biochemical and anthropometric assessment. Results showed that in any of the parameters evaluated, malnutrition was more severe among the patients with bacterial infections. Malnutrition was also more frequent among C cirrhotic patients (according to Child-Pugh classification). Moreover, there was a higher rate of death: 30% in the infected group versus 5.55% in the group presenting no bacterial infections (< 0.0001). The authors concluded that malnutrition is an important factor which may lead to the onset of bacterial infections, causing high death rate. Dietetic measures that may restore the nutritional status should be implemented early.

Momordica charantia and Allium sativum: Broad spectrum antibacterial activity

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Korean Journal of Pharmacognosy (South Korea), 1998, 29/3 (155-158)

In the Asian sub-continent *Momordica charantia* and *Allium sativum* are extensively used as food and are popular in herbal medicine. The two were screened against 15 pathogens and both exhibited broad spectrum antimicrobial activity. As compared to the standard antibiotics. *M. charantia* demonstrated broader and higher level of activity against most of the organisms. On the other hand *A. sativum* showed comparable activity to the standard antibiotics. Both *M. charantia* and *A. sativum* are proposed as non toxic, safe, broad spectrum antibacterial agents.

Partial purification and some properties of an antibacterial compound from Aloe vera

Levin H.; Hazenfratz R.; Friedman J.; Palevitch D.; Perl M. Agricultural Research Organization, The Volcani Center, Bet Dagan 50 250 Israel

Phytotherapy Research (United Kingdom) 1988, 2/2 (67-69)

Aqueous or ethanolic extracts of Aloe leaves were examined for antibacterial properties. The crude extrudes strongly stimulated bacterial growth. Separation of various fractions by thin layer chromatography (TLC) resulted in a fraction which inhibited the growth of *Bacillus subtilis*. A concomitant examination of protein and nucleic acid synthesis in *B. subtilis* in the presence of the inhibitory compound indicated that the plant extract inhibits primarily nucleic acid synthesis, after

which protein synthesis is also inhibited. The inhibitor seemed to be present in all examined Aloe species but at different concentrations. On a dry weight basis, the inhibitory effect was equally distributed between the skin and the gel fraction.

Activation of serum complement leads to inhibition of ascorbic acid transport

Padh H, Aleo JJ

Proc Soc Exp Biol Med 1987 Jun;185(2):153-7

Ascorbic acid is transported into 3T6 fibroblasts by a carrier-mediated, energy-dependent saturable active process with a $K(m)$ of 112 μ M and $V(max)$ of 158 pmole/min/mg protein. The transport is dependent on extracellular Nasup + concentration which reduces the $K(m)$. It was recently observed in this laboratory that bovine serum contained a heat-labile factor which, after interaction with bacterial endotoxin (lipopolysaccharides), inhibited ascorbic acid transport (J.J. Aleo and H. Padh, Proc Soc Exp Biol Med 179:128-131, 1985). We report here that the inhibition of ascorbic acid transport by endotoxin is mediated by the activation of serum complement. This was done by examining the activation of complement by other activators like zymosan and immunocomplexes (e.g., albumin and antibodies to albumin). Ascorbate transport was inhibited by the mixture of unheated serum and the activators. No inhibition was observed with serum devoid of C3 (component 3 of the complement). When C3-deficient serum was reconstituted by the addition of purified C3, the endotoxin-induced inhibition of ascorbate transport was restored. The implication of these findings is that in spite of a normal intake and blood level of the vitamin, tissues may not be getting adequate vitamin C during disease states when the complement in serum is activated. In other words, what may be considered an adequate intake of vitamin C under health conditions may not be adequate under disease conditions.

Effects of vitamins A, C, and E on aflatoxin Bsub 1-induced mutagenesis in Salmonella typhimurium TA-98 and TA-100

Raina V.; Gurtoo H.L.

Teratog Carcinog Mutagen 1985;5(1):29-40

The effects of retinoids (vitamin A analogs) and vitamins C and E on the aflatoxin Bsub 1-(AFBsub 1)-induced mutagenesis in Salmonella typhimurium TA-98 and TA-100 were investigated. The bioassay was performed under conditions that permitted the effects of vitamins on carcinogen metabolism to be assessed separately from effects on the expression of the mutated bacterial cell. Both retinoic acid and retinol inhibited (up to 50%) AFBsub 1-induced mutagenesis in S. typhimurium TA-98, but only retinol inhibited (up to 75%) mutagenesis in TA-100. Retinoic acid inhibition of mutagenesis in S. typhimurium TA-98 was pronounced over a wide concentration range (i.e., $2 \times 10^{sup -sup 10}$ to $2 \times 10^{sup -sup 8}$ M); however, at the higher concentrations (i.e., $2 \times 10^{sup -sup 8}$ to $2 \times 10^{sup -sup 6}$ M range) the predominant effect was the inhibition of the

metabolism of AFB₁ to its mutagenic metabolites. Vitamin E was more potent in inhibiting the expression of AFB₁-induced mutagenesis than vitamin C. However, the major inhibitory effects of vitamin E were related to the metabolism of AFB₁, whereas vitamin C was inhibitory at both metabolic and the post-metabolic levels of the AFB₁ mutagenesis assay. The results of these investigations suggest that vitamins A, C, or E inhibit both AFB₁ metabolism to its mutagenic metabolites as well as the expression of AFB₁-induced mutated bacterial cells.

Effect of vitamin A supplementation on lectin-induced diarrhoea and bacterial translocation in rats

Shoda R; Mahalanabis D(a); Islam K N; Wahed M A; Albert M J

Nutrition Research (USA), 1996, 16/3 (459-465)

In a rat model of lectin-induced diarrhoea with translocation of enteric bacteria into mesenteric lymph nodes we evaluated the role of prior vitamin A supplementation in correcting diarrhoea and bacterial translocation. Although intraperitoneal vitamin A palmitate injection (900 microg retinol equivalents twice a week for 5 weeks) substantially increased liver retinol concentration (154.83 plus or minus 23.57 vs 56.65 plus or minus 39.92 microg/< .01), it had no significant effect on faecal wet weight (2.64 plus or minus 1.21 vs 2.86 plus or minus 1.06 g/d), body weight loss (-36.7 plus or minus 16.7 vs -36.5 plus or minus 8.6 g/per 10 days) or rate of translocation (83% vs 100% positive) in supplemented rats compared to unsupplemented rats. However, the mean bacterial count in mesenteric lymph nodes was significantly reduced in vitamin A supplemented group (log colony forming units/g:3.53 plus or minus 0.77 vs 4.03 plus or minus 0.86, < .05). These findings suggest that vitamin A supplementation did not prevent diarrhoea and weight loss but reduced the severity of intestinal bacterial translocation to mesenteric lymph nodes in red kidney bean-induced diarrhoea and malabsorption. These results are compatible with the demonstrated effect of vitamin A supplementation in reducing childhood mortality in developing countries but with no effect on overall diarrhoea morbidity.

Increased translocation of Escherichia coli and development of arthritis in vitamin A-deficient rats

Wiedermann U, Hanson LA, Bremell T, Kahu H, Dahlgren UI Department of Clinical Immunology, University of Goteborg, Sweden.

Infection and Immunity (USA), 1995, 63/8 (3062-3068)

We studied the immune response and the colonization pattern in vitamin A-deficient rats that were colonized with the Escherichia coli O6 K13 pomp 21 strain, which is genetically manipulated to produce ovalbumin and to be resistant to ampicillin. In the vitamin A-deficient rats, the number of bacteria per gram of feces was about five times higher than in the paired fed control rats 4 weeks after colonization. In the control rats, the colon and the lower part of the ileum were

colonized, while in the vitamin A-deficient rats all parts of the small intestine, as well as the colon, were heavily inhabited by bacteria. Furthermore, in 75% of the vitamin A-deficient rats, the *E. coli* bacteria were found in the mesenteric lymph nodes, and in 50% of the rats *E. coli* were found in the kidneys. These animals also developed severe arthritis. The levels of serum immunoglobulin G (IgG), IgM, IgE, and biliary IgA antibodies against the bacterial antigens were significantly higher in the vitamin A-deficient rats than in the control rats. The number of IgA-producing cells in the lamina propria of the small intestine was significantly lower in the vitamin A-deficient rats than in the control rats; however, there was an increase in the number of CD8+ cells and transforming growth factor beta-producing cells in the lamina propria of the vitamin A-deficient rats. Disturbances in T-cell function were demonstrated, since spleen cells from the vitamin A-deficient rats produced more gamma interferon and interleukin-2 in vitro than control spleen cells. In summary, vitamin A deficiency led to a decrease in the ability to control the localization of intestinal bacteria and an increase in translocation, which was followed by development of arthritis regardless of substantial levels of antibacterial antibodies. The bacterial invasion made the animals hyperresponsive to the bacterial antigens, despite the fact that vitamin A deficiency is normally associated with suppressed antibody production, as previously shown by us and others.

Vitamin A supplementation improves macrophage function and bacterial clearance during experimental salmonella infection

Hatchigian EA, Santos JI, Broitman SA, Vitale JJ Department of Pathology, Boston University School of Medicine, Massachusetts 02118.

Proc. Soc. Exp. Biol. Med. (USA), 1989, 191/1 (47-54)

The effects of additional but nontoxic amounts of vitamin A on susceptibility to salmonella infection was studied by comparing rates of bacterial clearance and phagocytosis. Forty-eight male Lewis rats were divided into a treatment group receiving a total of 6000 units of vitamin A palmitate weekly for 5 weeks and a control group was given an equal volume of saline. After completion of the treatment regimen, one-half from each group were infected intraperitoneally with 10⁵ *Salmonella typhimurium*; the other half received intraperitoneal injection of saline. At this time no differences in weight gain were noted and all animals were sacrificed within 2 weeks. At 72 hr after bacterial challenge, all saline-treated control animals displayed bacteremia. Cultures of liver and splenic homogenates were positive in 89 and 100% of infected control animals vs 0 and 44% for treated animals during the first week of infection. Kupffer cell, peritoneal, and splenic macrophages of the vitamin A-treated group had greater phagocytic activity than controls as assessed by the percentage of cells ingesting yeast particles and by the number of particles ingested (phagocytic index). These results suggest that vitamin A in moderate amounts may benefit the host's response to infection by enhancing phagocytic cell function.

Inhibition by retinoic acid of multiplication of virulent tubercle bacilli in cultured human macrophages

Crowle AJ, Ross EJ Webb-Waring Lung Institute, University of Colorado, Health Sciences Center, Denver 80262.

Infect. Immun. (USA), 1989, 57/3 (840-844)

The immunologically active vitamin retinoic acid (RA) was tested for the ability to increase the resistance of cultured human macrophages (MP) to experimental infection with virulent *Mycobacterium tuberculosis* Erdman (tubercle bacilli (TB)). It was added to MP in various concentrations and addition regimens. Protection against TB was measured by counting live TB (CFU) in lysates of samples of MP taken at 0, 4, and 7 days after MP infection. RA was protective when added after infection at the pharmacologic concentration of 10^{-5} M and when added before infection at the physiologic concentration of 10^{-7} M. The protection lengthened intracellular generation times for TB, occasionally caused bacteriostasis, and regularly kept CFU counts at 7 days (end of the period of infection) 1 to 2 log₁₀ CFU below control values. Significant protection was seen in a series of 16 experiments with MP from seven different donors, but the degree of protection varied considerably. The protection depended partly on and was inversely proportional to concentrations of a serum substitute or autologous serum used as a supplement in the RPMI 1640 MP culture medium. It was strongest at concentrations of serum below 1%. RA at concentrations used in the MP cultures did not inhibit TB in the absence of MP. These results suggest that RA (vitamin A), like vitamin D, may have some immunoprotective role against human tuberculosis, as historically intimated by the regular use of vitamin A- and D-rich cod liver oil for the treatment of tuberculosis before the introduction of modern chemotherapy.

Antibacterial, antifungal, antiamebic, antiinflammatory and antipyretic studies on propolis bee products

Dobrowolski JW, Vohora SB, Sharma K, Shah SA, Naqvi SA, Dandiya PC
Institute of Management and Protection of Environment, Krakow, Poland.J
Ethnopharmacol. 1991 Oct;35(1):77-82

Propolis bee preparations revealed good antibacterial (particularly against Gram-positive bacteria), antifungal (against those responsible for superficial and dermatomycoses) and antiinflammatory (against acute and chronic models of inflammation) effects but no antiamebic or antipyretic capacity.

Antibacterial properties of propolis (bee glue)

Grange JM, Davey RW Department of Microbiology, National Heart & Lung Institute, London.

J R Soc Med. 1990 Mar;83(3):159-60. Review.

Propolis (bee glue) was found to have antibacterial activity against a range of commonly encountered cocci and Gram-positive rods, including the human tubercle bacillus, but only limited activity against Gram-negative bacilli. These

findings confirm previous reports of antimicrobial properties of this material, possibly attributable to its high flavonoid content.

Biological properties and clinical application of propolis. III. Investigation of the sensitivity of staphylococci isolated from pathological cases to ethanol extract of propolis (EEP)

Scheller S, Tustanowski J, Kurylo B, Paradowski Z, Obuszko Z

Arzneimittelforschung. 1977 Jul;27(7):1395.

Staphylococci isolated from pathological material exhibited a reduced sensitivity to ethanol extract of propolis (EEP) in 90% of cases. No cross-resistance of the staphylococci to EEP and to any commonly used antibiotics was found. The induction of resistance to EEP in laboratory strain of *Staphylococcus aureus* (Oxford 209 P) can be achieved already after serial passages on nutrient media containing EEP. Culturing *Staphylococcus* resistant to EEP in an environment devoid of this compound caused a remission to sensitivity of the strain investigated.

Biological properties and clinical application of propolis. I. Some physico-chemical properties of propolis

Scheller S, Szaflarski J, Tustanowski J, Nolewajka E, Stojko A

Arzneimittelforschung. 1977;27(4):889-90

The presence of 19 elements has been shown in the ethanol extracts of propolis (EEP). Three fractions have been obtained by filtration through a structural gel that did not show an initial antibacterial activity when investigated separately. Fractions 2 and 3 joined together have regained this activity. EEP solutions maintain their antibacterial activity in acidic or neutral pH. Insensitivity of EEP solutions on temperature of 75°C for 30 min has been found.

Oral administration of bovine lactoferrin for treatment of tinea pedis. A placebo-controlled, double-blind study.

Yamauchi K, Hiruma M, Yamazaki N, Wakabayashi H, Kuwata H, Teraguchi S, Hayasawa H, Suegara N, Yamaguchi H. Nutritional Science Laboratory, Morinaga Milk Industry Co., Ltd, Kanagawa, Japan.

Mycoses 2000;43(5):197-202

A clinical study was conducted to evaluate the effectiveness of lactoferrin, which is a protein component of cow's milk, in the treatment of tinea pedis. Doses of either 600 mg or 2000 mg of lactoferrin, or a placebo was orally administered daily for 8 weeks to 37 adults who were judged to have mild or moderate tinea pedis. Dermatological improvement and antifungal efficacy were assessed. In the analysis of all subjects, dermatological symptoms scores in all groups decreased

but the differences were not statistically significant comparing the three groups. However, in the analysis limited to subjects with moderate vesicular or interdigital tinea pedis, dermatological symptoms scores in the lactoferrin-treated groups decreased significantly in comparison with the placebo group (< 0.05). The organisms isolated were *Trichophyton rubrum* and *Trichophyton mentagrophytes*. A mycological cure was not seen in any of the subjects. In the 37 subjects there were no adverse events and no subject withdrew from the study because of an adverse event. These results suggest that orally administered lactoferrin can improve the dermatological symptoms in some subjects. The potential usefulness of lactoferrin as a functional food material for treating tinea pedis was seen for the first time in this study.

Lactoferrin protects gut mucosal integrity during endotoxemia induced by lipopolysaccharide in mice.

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Inflammation 2000 Feb;24(1):33-44

The hypothesis that lactoferrin protects mice against lethal effects of bacterial lipopolysaccharide (LPS) is the subject of experimental investigations described in this article. Lipopolysaccharide is a powerful toxin produced by gram negative bacteria that when injected into humans or experimental animals reproduce many of the pathophysiologic and immune responses caused by live bacteria. Lactoferrin administered intraperitoneally 1 hr prior to injection of LPS significantly enhanced the survival of mice, reducing LPS-induced mortality from 83.3% to 16.7%. Changes in locomotor and other behavioral activities resulting from LPS injection were not present in mice treated with lactoferrin. Also, histological examination of intestine revealed remarkable resistance to injury produced by LPS if mice were pretreated with lactoferrin. Severe villus atrophy, edema and epithelial vacuolation were observed in LPS-treated animals but not in lactoferrin-treated counterparts. Electrophysiological parameters were used to assess secretory and absorptive functions in the small intestine. In mice treated with LPS, transmural electrical resistance was reduced and absorption of glucose was increased. Lactoferrin treatment had no significant influence on basal electrophysiological correlates of net ion secretion or glucose absorption nor on changes induced by LPS. Collectively, these results suggest that lactoferrin attenuates the lethal effect of LPS and modulates behavioral and histopathological sequela of endotoxemia.

10. Breast Cancer

Preventative and curative options include:

Indole-3-carbinol, curcumin, green tea extract, CLA or CLA with Guarana, sulphoraphane, se-methylselenocysteine, CoQ10, fish oil, vitamin D3, vitamin A, vitamin E succinate, gamma E Tocopherol/Tocotrienol, vitamin C, linolenic acid, whey protein concentrate-isolate, calcium, magnesium, vitamin K, silicon, multinutrients, melatonin, selenium.

Curcumin is an in vivo inhibitor of angiogenesis.

Arbiser JL, Klauber N, Rohan R, van Leeuwen R, Huang MT, Fisher C, Flynn E, Byers HR. Department of Dermatology, Harvard Medical School, Boston, Massachusetts, USA. jlarbiser@bics.bwh.harvard.edu

Mol Med 1998 Jun;4(6):376-83

BACKGROUND: Curcumin is a small-molecular-weight compound that is isolated from the commonly used spice turmeric. In animal models, curcumin and its derivatives have been shown to inhibit the progression of chemically induced colon and skin cancers. The genetic changes in carcinogenesis in these organs involve different genes, but curcumin is effective in preventing carcinogenesis in both organs. A possible explanation for this finding is that curcumin may inhibit angiogenesis.

MATERIALS AND METHODS: Curcumin was tested for its ability to inhibit the proliferation of primary endothelial cells in the presence and absence of basic fibroblast growth factor (bFGF), as well as its ability to inhibit proliferation of an immortalized endothelial cell line. Curcumin and its derivatives were subsequently tested for their ability to inhibit bFGF-induced corneal neovascularization in the mouse cornea. Finally, curcumin was tested for its ability to inhibit phorbol ester-stimulated vascular endothelial growth factor (VEGF) mRNA production.

RESULTS: Curcumin effectively inhibited endothelial cell proliferation in a dose-dependent manner. Curcumin and its derivatives demonstrated significant inhibition of bFGF-mediated corneal neovascularization in the mouse. Curcumin had no effect on phorbol ester-stimulated VEGF production.

CONCLUSIONS: These results indicate that curcumin has direct antiangiogenic activity in vitro and in vivo. The activity of curcumin in inhibiting carcinogenesis in diverse organs such as the skin and colon may be mediated in part through angiogenesis inhibition.

The dietary pigment curcumin reduces endothelial tissue factor gene expression by inhibiting binding of AP-1 to the DNA and activation of NF-kappa B.

Bierhaus A, Zhang Y, Quehenberger P, Luther T, Haase M, Muller M, Mackman N, Ziegler R, Nawroth PP. Department of Internal Medicine I, University of Heidelberg, Germany.

Thromb Haemost 1997 Apr;77(4):772-82

The natural occurring pigment curcumin, a major component of the spice tumeric, has been described to have antioxidative, anti-tumorpromoting, anti-thrombotic and anti-inflammatory properties. It appears, that the pleiotropic effects of curcumin are at least partly due to inhibition of the transcription factors NF-kappa B and AP-1. This study investigates the effect of curcumin on the TNF alpha induced expression of endothelial Tissue Factor (TF), the central mediator of coagulation known to be controlled by AP-1 and NF-kappa B. When bovine aortic endothelial cells (BAEC) were preincubated in the presence of curcumin, TNF alpha induced TF gene transcription and expression were reduced. Transient transfection studies with TF-promoter plasmids revealed that both, NF-kappa B and AP-1 dependent TF expression, were reduced by curcumin action. The observed inhibitions were due to distinct mechanisms. Curcumin inhibited TNF alpha induced I kappa B alpha degradation and the nuclear import of NF-kappa B. In contrast, inhibition of AP-1 was due to a direct interaction of curcumin with AP-1-binding to its DNA binding motif. Thus, curcumin inhibits NF-kappa B and AP-1 by two different mechanisms and reduces expression of endothelial genes controlled by both transcription factors in vitro.

Coenzymes Q: stimulants of the phagocytic activity in rats and immune response in mice.

Bliznakov, E., Casey, A., Premuzic, E.

Experientia 1970: 26(9): 953-4.

No Abstract

Fruit, vegetables, and cancer prevention: a review of the epidemiological evidence.

Block G, Patterson B, Subar A. Dept. of Social and Administrative Health Sciences, School of Public Health, University of California, Berkeley 94720.

Nutr Cancer 1992;18(1):1-29

Approximately 200 studies that examined the relationship between fruit and vegetable intake and cancers of the lung, colon, breast, cervix, esophagus, oral cavity, stomach, bladder, pancreas, and ovary are reviewed. A statistically significant protective effect of fruit and vegetable consumption was found in 128

of 156 dietary studies in which results were expressed in terms of relative risk. For most cancer sites, persons with low fruit and vegetable intake (at least the lower one-fourth of the population) experience about twice the risk of cancer compared with those with high intake, even after control for potentially confounding factors. For lung cancer, significant protection was found in 24 of 25 studies after control for smoking in most instances. Fruits, in particular, were significantly protective in cancers of the esophagus, oral cavity, and larynx, for which 28 of 29 studies were significant. Strong evidence of a protective effect of fruit and vegetable consumption was seen in cancers of the pancreas and stomach (26 of 30 studies), as well as in colorectal and bladder cancers (23 of 38 studies). For cancers of the cervix, ovary, and endometrium, a significant protective effect was shown in 11 of 13 studies, and for breast cancer a protective effect was found to be strong and consistent in a meta analysis. It would appear that major public health benefits could be achieved by substantially increasing consumption of these foods.

Effects of dietary indole-3-carbinol on estradiol metabolism and spontaneous mammary tumors in mice.

Bradlow HL, Michnovicz J, Telang NT, Osborne MP. Institute for Hormone Research, New York, NY 10016.

Carcinogenesis 1991 Sep;12(9):1571-4

Indole-3-carbinol (I3C) is a potent inducer of cytochrome P450 enzymes in many species, including humans. We therefore studied alterations in the cytochrome P450-dependent metabolism of estradiol in different strains of mice consuming I3C in semisynthetic powdered diets at doses ranging from 250 to 5000 p.p.m. (34-700 mg/kg/day) for different periods of time. In short-term metabolic studies (3 weeks), wet liver weight increased in SW and C3H/OuJ mice in a dose-responsive manner. Dietary I3C increased the cytochrome P450 content measured in hepatic microsomes, as well as the extent of estradiol 2-hydroxylation, up to 5-fold. In a long-term feeding experiment (8 months), female C3H/OuJ mice consumed synthetic diets containing I3C at 0, 500 or 2000 p.p.m. Mammary tumor incidence and multiplicity were significantly lower at both doses of I3C, and tumor latency was prolonged in the high-dose group. We conclude that I3C is an inducer of hepatic P450-dependent estrogen metabolism in mice, and that it is chemopreventive in the C3H/OuJ mouse mammary tumor model. This protective effect may be mediated in part by the increased 2-hydroxylation and consequent inactivation of endogenous estrogens.

Indole-3-carbinol and diindolylmethane as aryl hydrocarbon (Ah) receptor agonists and antagonists in T47D human breast cancer cells.

Chen I, Safe S, Bjeldanes L. Veterinary Physiology and Pharmacology, Texas A&M University, College Station 77843-4466, USA.

Biochem Pharmacol 1996 Apr 26;51(8):1069-76

Indole-3-carbinol (I3C) is a major component of Brassica vegetables, and diindolylmethane (DIM) is the major acid-catalyzed condensation product derived from I3C. Both compounds competitively bind to the aryl hydrocarbon (Ah) receptor with relatively low affinity. In Ah-responsive T47D human breast cancer cells, I3C and DIM did not induce significantly CYP1A1-dependent ethoxyresorufin O-deethylase (EROD) activity or CYP1A1 mRNA levels at concentrations as high as 125 or 31 microM, respectively. A 1 nM concentration of 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) induced EROD activity in these cells, and cotreatment with TCDD plus different concentrations of I3C (1-125 microM) or DIM (1-31 microM) resulted in a < 90% decrease in the induced response at the highest concentration of I3C or DIM. I3C or DIM also partially inhibited (< 50%) induction of CYP1A1 mRNA levels by TCDD and reporter gene activity, using an Ah-responsive plasmid construct in transient transfection assays. In T47D cells cotreated with 5 nM [³H]TCDD alone or in combination with 250 microM I3C or 31 microM DIM, there was a 37 and 73% decrease, respectively, in formation of the nuclear Ah receptor. The more effective inhibition of induced EROD activity by I3C and DIM was due to in vitro inhibition of enzyme activity. Thus, both I3C and DIM are partial Ah receptor antagonists in the T47D human breast cancer cell line.

Prevention by coenzyme Q10 of the electrocardiographic changes induced by adriamycin in rats.

Choe JY, Combs AB, Folkers K.

Res Commun Chem Pathol Pharmacol 1979 Jan;23(1):199-202

The administration of adriamycin (ADM) to rats has consistently caused a widening of the QRS complex of the electrocardiogram. When coenzyme Q10 was also administered, beginning two days before ADM, this widening of the QRS complex and the elongation of the Q-T interval were reduced or totally prevented, depending upon conditions. ADM alone or with coenzyme Q10 did not alter the P-R interval. Some control by coenzyme Q10 of the cardiotoxicity of adriamycin in cancer patients is promising.

Reduction by coenzyme Q10 of the acute toxicity of adriamycin in mice.

Combs AB, Choe JY, Truong DH, Folkers K.

Res Commun Chem Pathol Pharmacol 1977 Nov;18(3):565-8

Pretreatment for four days with coenzyme Q10 (COQ10) reduced the acute toxicity in mice treated with adriamycin. In two sequential protocols, adriamycin allowed only 36 and 42% survival, respectively. Pretreatment with COQ10 allowed 80 and 86% survival, respectively. The differences are significant, p less than 0.05. The mechanism for this reduction in the acute toxicity may be based upon the prevention by the supplementary COQ10 of the inhibition caused by adriamycin to COQ10-dependent enzymes in cardiac and other tissues. The

prospect of diminishing the toxicity of adriamycin in cancer patients remains promising and important.

Indole-3-carbinol inhibits the expression of cyclin-dependent kinase-6 and induces a G1 cell cycle arrest of human breast cancer cells independent of estrogen receptor signaling.

Cover CM, Hsieh SJ, Tran SH, Hallden G, Kim GS, Bjeldanes LF, Firestone GL. Department of Molecular and Cell Biology and Cancer Research Laboratory, University of California, Berkeley, California 94720, USA.

J Biol Chem 1998 Feb 13;273(7):3838-47

Indole-3-carbinol (I3C), a naturally occurring component of Brassica vegetables such as cabbage, broccoli, and Brussels sprouts, has been shown to reduce the incidence of spontaneous and carcinogen-induced mammary tumors. Treatment of cultured human MCF7 breast cancer cells with I3C reversibly suppresses the incorporation of [3H]thymidine without affecting cell viability or estrogen receptor (ER) responsiveness. Flow cytometry of propidium iodide-stained cells revealed that I3C induces a G1 cell cycle arrest. Concurrent with the I3C-induced growth inhibition, Northern blot and Western blot analyses demonstrated that I3C selectively abolished the expression of cyclin-dependent kinase 6 (CDK6) in a dose- and time-dependent manner. Furthermore, I3C inhibited the endogenous retinoblastoma protein phosphorylation and CDK6 phosphorylation of retinoblastoma in vitro to the same extent. After the MCF7 cells reached their maximal growth arrest, the levels of the p21 and p27 CDK inhibitors increased by 50%. The antiestrogen tamoxifen also suppressed MCF7 cell DNA synthesis but had no effect on CDK6 expression, while a combination of I3C and tamoxifen inhibited MCF7 cell growth more stringently than either agent alone. The I3C-mediated cell cycle arrest and repression of CDK6 production were also observed in estrogen receptor-deficient MDA-MB-231 human breast cancer cells, which demonstrates that this indole can suppress the growth of mammary tumor cells independent of estrogen receptor signaling. Thus, our observations have uncovered a previously undefined antiproliferative pathway for I3C that implicates CDK6 as a target for cell cycle control in human breast cancer cells. Moreover, our results establish for the first time that CDK6 gene expression can be inhibited in response to an extracellular antiproliferative signal.

Indole-3-carbinol and tamoxifen cooperate to arrest the cell cycle of MCF-7 human breast cancer cells.

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Cancer Res 1999 Mar 15;59(6):1244-51

The current options for treating breast cancer are limited to excision surgery, general chemotherapy, radiation therapy, and, in a minority of breast cancers that

rely on estrogen for their growth, antiestrogen therapy. The naturally occurring chemical indole-3-carbinol (I3C), found in vegetables of the Brassica genus, is a promising anticancer agent that we have shown previously to induce a G1 cell cycle arrest of human breast cancer cell lines, independent of estrogen receptor signaling. Combinations of I3C and the antiestrogen tamoxifen cooperate to inhibit the growth of the estrogen-dependent human MCF-7 breast cancer cell line more effectively than either agent alone. This more stringent growth arrest was demonstrated by a decrease in adherent and anchorage-independent growth, reduced DNA synthesis, and a shift into the G1 phase of the cell cycle. A combination of I3C and tamoxifen also caused a more pronounced decrease in cyclin-dependent kinase (CDK) 2-specific enzymatic activity than either compound alone but had no effect on CDK2 protein expression. Importantly, treatment with I3C and tamoxifen ablated expression of the phosphorylated retinoblastoma protein (Rb), an endogenous substrate for the G1 CDKs, whereas either agent alone only partially inhibited endogenous Rb phosphorylation. Several lines of evidence suggest that I3C works through a mechanism distinct from tamoxifen. I3C failed to compete with estrogen for estrogen receptor binding, and it specifically down-regulated the expression of CDK6. These results demonstrate that I3C and tamoxifen work through different signal transduction pathways to suppress the growth of human breast cancer cells and may, therefore, represent a potential combinatorial therapy for estrogen-responsive breast cancer.

Characterization of the biological activity of gamma-glutamyl-Se-methylselenocysteine: a novel, naturally occurring anticancer agent from garlic.

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Cancer Res 2001 Apr 1;61(7):2923-8

Gamma-glutamyl-Se-methylselenocysteine (GGMSC) has recently been identified as the major Se compound in natural garlic and selenized garlic. Our working hypothesis is that GGMSC serves primarily as a carrier of Se-methylselenocysteine (MSC), which has been demonstrated in past research to be a potent cancer chemopreventive agent in animal carcinogenesis bioassays. The present study was designed to examine the in vivo responses to GGMSC or MSC using a variety of biochemical and biological end points, including (a) urinary Se excretion as a function of bolus dose; (b) tissue Se accumulation profile; (c) anticancer efficacy; and (d) gene expression changes as determined by cDNA array analysis. Our results showed that like MSC, GGMSC was well absorbed p.o., with urinary excretion as the major route for eliminating excess Se. When fed chronically, the profile of Se accumulation in various tissues was very comparable after treatment with either GGMSC or MSC. In rats that had been challenged with a carcinogen, supplementation with either GGMSC or MSC resulted in a lower prevalence of premalignant lesions in the mammary gland, and fewer mammary carcinomas when these early lesions were allowed to progress. More importantly, we found that a short term GGMSC/MSC treatment schedule of 4 weeks immediately after carcinogen dosing was sufficient to provide

significant cancer protection, even in the absence of a sustained exposure past the initial 4-week period. With the use of the Clontech Atlas Rat cDNA Array, we further discovered that the gene expression changes induced in mammary epithelial cells of rats that were given either GGMSC or MSC showed a high degree of concordance. On the basis of the collective biology, biochemistry, and molecular biology data, we conclude that GGMSC is an effective anticancer agent with a mechanism of action very similar to that of MSC.

The chemoprevention of cancer by mevalonate-derived constituents of fruits and vegetables.

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J Nutr 1994 May;124(5):607-14

Anutritive isoprenoid constituents of fruits, vegetables, cereal grains and essential oils exhibit a spectrum of anticarcinogenic activities. The induction of hepatic Phase II detoxifying activities by dietary isoprenoids appears to underlie their blocking action. The second anticarcinogenic action of the dietary isoprenoids, suppression of the growth of chemically initiated and transplanted tumors is, we suggest, secondary to the inhibition of mevalonate pathway activities. Mevinolin, a competitive inhibitor of 3-hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase activity, depletes cells of the intermediate products of the pathway that are required for the posttranslational modification of proteins, a process giving the proteins lipophilic anchors that bind to membranes. As a consequence, nuclear lamins and ras oncoproteins remain in nascent states, and cells do not proliferate. gamma-Tocotrienol, perillyl alcohol, geraniol and d-limonene suppress hepatic HMG-CoA reductase activity, a rate-limiting step in cholesterol synthesis, and modestly lower serum-cholesterol levels of animals. These isoprenoids also suppress tumor growth. The HMG-CoA reductase of neoplastic tissues differs from that of sterologenic tissues in being markedly resistant to sterol feedback inhibition. Our review suggests that the mevalonate pathway of tumor tissues is uniquely sensitive to the inhibitory actions of the dietary isoprenoids.

Relevance of the biosynthesis of coenzyme Q10 and of the four bases of DNA as a rationale for the molecular causes of cancer and a therapy.

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Biochem Biophys Res Commun 1996 Jul 16;224(2):358-61

In the human, coenzyme Q10 (vitamin Q10) is biosynthesized from tyrosine through a cascade of eight aromatic precursors. These precursors indispensably require eight vitamins, which are tetrahydrobiopterin, vitamins B6, C, B2, B12, folic acid, niacin, and pantothenic acid as their coenzymes. Three of these eight vitamins (the coenzyme B6, and the coenzymes niacin and folic acid) are indispensable in the biosynthesis of the four bases (thymidine, guanine, adenine,

and cytosine) of DNA. One or more of the three vitamins required for DNA are known to cause abnormal pairing of the four bases, which can then result in mutations and the diversity of cancer. The coenzyme B6, required for the conversion of tyrosine to p-hydroxybenzoic acid, is the first coenzyme required in the cascade of precursors. A deficiency of the coenzyme B6 can cause dysfunctions, prior to the formation of vitamin Q10, to DNA. Former data on blood levels of Q10 and new data herein on blood levels of B6, measured as EDTA, in cancer patients established deficiencies of Q10 and B6 in cancer. This complete biochemistry relating to biosyntheses of Q10 and the DNA bases is a rationale for the therapy of cancer with Q10 and other entities in this biochemistry.

Chemoprevention of chemically-induced mammary carcinogenesis by indole-3-carbinol.

Grubbs CJ, Steele VE, Casebolt T, Juliana MM, Eto I, Whitaker LM, Dragnev KH, Kelloff GJ, Lubet RL. Department of Nutrition Sciences, University of Alabama at Birmingham 35924, USA.

Anticancer Res 1995 May-Jun;15(3):709-16

Indole-3-carbinol, a component of cruciferous vegetables, was evaluated for its efficacy in the prevention of chemically-induced mammary tumors using three different protocols. Because this compound was unstable, it was administered by gavage rather than in the diet. A preliminary dose range study revealed that dose levels of 100 and 50 mg/day, 5x/week, were not toxic to female Sprague-Dawley rats. Initial studies in the DMBA model showed that administering indole-3-carbinol during the initiation and promotion phases were highly effective chemopreventive methods (91-96% reduction in cancer multiplicity). Subsequent studies showed that the administration of indole-3-carbinol only during the initiation phase (7 days prior to until 7 days post DMBA) was also highly effective as a chemopreventive agent. Determination of enzyme levels in the livers of animals treated long-term with indole-3-carbinol showed high levels of induction of various phase I and phase II drug metabolizing enzymes. Finally, indole-3-carbinol when administered both prior to and after MNU (a direct acting carcinogen) caused a significant decrease (65%) in mammary tumor multiplicity. These results support previous studies that indole-3-carbinol can prevent mammary carcinogenesis by direct and indirect acting carcinogens. Therefore, indole-3-carbinol might be a good candidate for chemoprevention of breast cancer in women.

Inhibition of proliferation of estrogen receptor-negative MDA-MB-435 and -positive MCF-7 human breast cancer cells by palm oil tocotrienols and tamoxifen, alone and in combination.

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J Nutr 1997 Mar;127(3):544S-548S

Tocotrienols are a form of vitamin E, having an unsaturated isoprenoid side-chain rather than the saturated side-chain of tocopherols. The tocotrienol-rich fraction (TRF) from palm oil contains alpha-tocopherol and a mixture of alpha-, gamma- and delta-tocotrienols. Earlier studies have shown that tocotrienols display anticancer activity. We previously reported that TRF, alpha-, gamma- and delta-tocotrienols inhibited proliferation of estrogen receptor-negative MDA-MB-435 human breast cancer cells with 50% inhibitory concentrations (IC₅₀) of 180, 90, 30 and 90 microg/mL, respectively, whereas alpha-tocopherol had no effect at concentrations up to 500 microg/mL. Further experiments with estrogen receptor-positive MCF-7 cells showed that tocotrienols also inhibited their proliferation, as measured by [³H] thymidine incorporation. The IC₅₀s for TRF, alpha-tocopherol, alpha-, gamma- and delta-tocotrienols were 4, 125, 6, 2 and 2 microg/mL, respectively. Tamoxifen, a widely used synthetic antiestrogen inhibits the growth of MCF-7 cells with an IC₅₀ of 0.04 microg/mL. We tested 1:1 combinations of TRF, alpha-tocopherol and the individual tocotrienols with tamoxifen in both cell lines. In the MDA-MB-435 cells, all of the combinations were found to be synergistic. In the MCF-7 cells, only 1:1 combinations of gamma- or delta-tocotrienol with tamoxifen showed a synergistic inhibitory effect on the proliferative rate and growth of the cells. The inhibition by tocotrienols was not overcome by addition of excess estradiol to the medium. These results suggest that tocotrienols are effective inhibitors of both estrogen receptor-negative and -positive cells and that combinations with tamoxifen should be considered as a possible improvement in breast cancer therapy.

Suppression of c-Jun/AP-1 activation by an inhibitor of tumor promotion in mouse fibroblast cells.

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Proc Natl Acad Sci U S A 1991 Jun 15;88(12):5292-6

Curcumin, a dietary pigment responsible for the yellow color of curry, is a potent inhibitor of tumor promotion by phorbol esters. Functional activation of transcriptional factor c-Jun/AP-1 is believed to play an important role in signal transduction of phorbol 12-myristate 13-acetate-induced tumor promotion. Suppression of the c-Jun/AP-1 activation by curcumin is observed in mouse fibroblast cells. In vitro experiments indicate that inhibition of c-Jun/AP-1 binding to its cognate motif by curcumin may be responsible for the inhibition of c-Jun/AP-1-mediated gene expression. These findings show that the effect of curcumin on phorbol 12-myristate 13-acetate-induced inflammation/tumor promotion could be studied at the molecular level.

Comparison of selenium and sulfur analogs in cancer prevention.

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Carcinogenesis 1992 Jul;13(7):1167-70

Several organoselenium compounds have been shown to have powerful anticarcinogenic activity. In view of certain similarities between selenium and sulfur biochemistry, we have evaluated the chemopreventive efficacy of three pairs of analogs using the 7,12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumor model in rats. The compounds tested were selenocystamine/cysteamine, S-methylselenocysteine/S-methylcysteine, selenobetaine/sulfobetaine. In the first study, each agent was added to the basal AIN-76A diet and was given before and continued after DMBA treatment until the end. All three selenium compounds were active; a 50% inhibition was achieved at approximately 25×10^{-6} mol/kg with S-methylselenocysteine and selenobetaine and at approximately 40×10^{-6} mol/kg with selenocystamine. In the sulfur series, only cysteamine and S-methylcysteine produced anticancer activity, and the levels required for comparable responses were 500- to 750-fold higher compared to the corresponding selenium analogs. Sulfobetaine was inactive even when present at near maximally tolerated levels. In the second study, S-methylselenocysteine and S-methylcysteine were chosen for further examination during the initiation and post-initiation phases of mammary carcinogenesis. S-methylselenocysteine was effective when it was given either before or after DMBA administration. In contrast, S-methylcysteine was effective only after DMBA treatment. Thus, compared to the sulfur structural analogs, selenium compounds are much more active in cancer protection and may have a multi-modal mechanism in preventing cellular transformation as well as in delaying or inhibiting the expression of malignancy after carcinogen exposure.

Conjugated linoleic acid-enriched butter fat alters mammary gland morphogenesis and reduces cancer risk in rats.

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J Nutr 1999 Dec;129(12):2135-42

Conjugated linoleic acid (CLA) is a potent cancer preventive agent in animal models. To date, all of the in vivo work with CLA has been done with a commercial free fatty acid preparation containing a mixture of c9,t11-, t10,c12- and c11,t13-isomers, although CLA in food is predominantly (80-90%) the c9,t11-isomer present in triacylglycerols. The objective of this study was to determine whether a high CLA butter fat has biological activities similar to those of the mixture of free fatty acid CLA isomers. The following four different endpoints were evaluated in rat mammary gland: 1) digitized image analysis of epithelial mass in mammary whole mount; 2) terminal end bud (TEB) density; 3) proliferative activity of TEB cells as determined by proliferating cell nuclear antigen immunohistochemistry; and 4) mammary cancer prevention bioassay in the methylnitrosourea model. It should be noted that TEB cells are the target cells for mammary chemical carcinogenesis. Feeding butter fat CLA to rats during the time of pubescent mammary gland development reduced mammary epithelial mass by 22%, decreased the size of the TEB population by 30%, suppressed the proliferation of TEB cells by 30% and inhibited mammary tumor yield by 53% (P

< 0.05). Furthermore, all of the above variables responded with the same magnitude of change to both butter fat CLA and the mixture of CLA isomers at the level of CLA (0.8%) present in the diet. Interestingly, there appeared to be some selectivity in the uptake or incorporation of c9,t11-CLA over t10,c12-CLA in the tissues of rats given the mixture of CLA isomers. Rats consuming the CLA-enriched butter fat also consistently accumulated more total CLA in the mammary gland and other tissues (four- to sixfold increases) compared with those consuming free fatty acid CLA (threefold increases) at the same dietary level of intake. We hypothesize that the availability of vaccenic acid (t11-18:1) in butter fat may serve as the precursor for the endogenous synthesis of CLA via the Delta9-desaturase reaction. Further studies will be conducted to investigate other attributes of this novel dairy product.

Methylselenocysteine modulates proliferation and apoptosis biomarkers in premalignant lesions of the rat mammary gland.

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Anticancer Res 2001 Mar-Apr;21(2A):863-7

In the rat mammary carcinogenesis model, premalignant lesions known as intraductal proliferations (IDPs) are detectable within a few weeks after carcinogen treatment. These early transformed colonies are the precursors for the eventual formation of carcinomas. Our past research indicated that methylselenocysteine added to the diet of rats reduced the development of IDPs of all sizes (the size of each IDP was estimated operationally by the number of 5-micron serial sections showing the same pathology). The appearance of an IDP lesion represents a balance between cell proliferation and cell death. The modulation of these two cellular events by methylselenocysteine was investigated. The abdominal-inguinal mammary gland was excised 6 weeks after MNU administration. Proliferation and apoptosis were evaluated by BrdU labeling and the TUNEL assay, respectively. The expression levels of several cell cycle and apoptosis regulatory proteins, including cyclin D1, cyclin A, p27, p16, bcl-2, box and bak, were also assessed. All of the above endpoints were quantified by immunohistochemistry in paraffin-embedded sections. The results showed that the magnitude of the response to methylselenocysteine intervention seemed to depend on the size of the IDP lesion. For the purpose of this study, the small and large lesions were classified as those containing < or = 30 or > 30 serial sections, respectively. With the small lesions, methylselenocysteine significantly inhibited BrdU labeling and the expression of cyclin D1 and cyclin A, but increased the expression of p27. Interesting, only p27 was upregulated in the larger IDP lesions, while BrdU labeling and the cyclins were not affected. It is possible that the transformed phenotype becomes less sensitive to selenium-mediated arrest of proliferation once it progresses to a more advanced pathological stage. In contrast, methylselenocysteine stimulated apoptosis (TUNEL assay) by 3 to 4 fold, and this increase was evident in both the small and large IDP lesions. Consistent with the induction of apoptosis, a reduced

expression of bcl-2 was also observed in the methylselenocysteine group. In summary, our data suggest that exposure to methylselenocysteine blocks clonal expansion of premalignant lesions at an early stage. This is achieved by simultaneously modulating certain molecular pathways that are responsible for inhibiting cell proliferation and enhancing apoptosis.

Chemoprevention of mammary cancer with Se-allylselenocysteine and other selenoamino acids in the rat.

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Anticancer Res 1999 Jul-Aug;19(4B):2875-80

The present study examined the mammary cancer chemopreventive activity of Se-methylselenocysteine, Se-propylselenocysteine and Se-allylselenocysteine in the rat methylnitrosourea (MNU) model. Each compound was supplemented in the diet at a level of 2 ppm Se for the entire duration of the experiment after MNU dosing. Se-Allylselenocysteine was the most active and caused a reduction in total tumor yield by 86%. Se-Methylselenocysteine and Se-propylselenocysteine were similar but less effective, and both produced a decrease of about 50% in tumorigenesis. All three compounds were very well absorbed through the gastrointestinal tract. However, more selenium was excreted in urine after gavaging with Se-propylselenocysteine or Se-allylselenocysteine compared with Se-methylselenocysteine. Analysis of selenium in the mammary gland and other organs showed that tissue selenium levels did not appear to be correlated with differences in chemopreventive activity. A lyase activity capable of catalyzing scission of the Se-alkyl group from the remainder of the amino acid was demonstrated. This activity was found to be high in liver and kidney, but relatively low in mammary gland and intestine. Minimal variations in enzyme activity towards each of the substrates were observed. Our results support the concept that Se-alkylselenoamino acids could be used as precursors for delivering the Se-alkyl moiety and that intrinsic chemical differences in the Se-alkyl substituent of the test compounds are likely to be important determinants of their biological effects.

Conjugated linoleic acid inhibits proliferation and induces apoptosis of normal rat mammary epithelial cells in primary culture.

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Exp Cell Res 1999 Jul 10;250(1):22-34

The trace fatty acid conjugated linoleic acid (CLA) inhibits rat mammary carcinogenesis when fed prior to carcinogen during pubertal mammary gland development or during the promotion phase of carcinogenesis. The following

studies were done to investigate possible mechanisms of these effects. Using a physiological model for growth and differentiation of normal rat mammary epithelial cell organoids (MEO) in primary culture, we found that CLA, but not linoleic acid (LA), inhibited growth of MEO and that this growth inhibition was mediated both by a reduction in DNA synthesis and a stimulation of apoptosis. The effects of CLA did not appear to be mediated by changes in epithelial protein kinase C (PKC) since neither total activity nor expression nor localization of PKC isoenzymes alpha, betaII, delta, varepsilon, eta, or zeta were altered in the epithelium of CLA-fed rats. In contrast, PKCs delta, varepsilon, and eta were specifically upregulated and associated with a lipid-like, but acetone-insoluble, fibrillar material found exclusively in adipocytes from CLA-fed rats. Taken together, these observations demonstrate that CLA can act directly to inhibit growth and induce apoptosis of normal MEO and may thus prevent breast cancer by its ability to reduce mammary epithelial density and to inhibit the outgrowth of initiated MEO. Moreover, the changes in mammary adipocyte PKC expression and lipid composition suggest that the adipose stroma may play an important in vivo role in mediating the ability of CLA to inhibit mammary carcinogenesis. Copyright 1999 Academic Press.

Curcumin induces a p53-dependent apoptosis in human basal cell carcinoma cells.

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J Invest Dermatol 1998 Oct;111(4):656-61

Curcumin, a potent antioxidant and chemopreventive agent, has recently been found to be capable of inducing apoptosis in human hepatoma and leukemia cells by way of an elusive mechanism. Here, we demonstrate that curcumin also induces apoptosis in human basal cell carcinoma cells in a dose- and time-dependent manner, as evidenced by internucleosomal DNA fragmentation and morphologic change. In our study, consistent with the occurrence of DNA fragmentation, nuclear p53 protein initially increased at 12 h and peaked at 48 h after curcumin treatment. Prior treatment of cells with cycloheximide or actinomycin D abolished the p53 increase and apoptosis induced by curcumin, suggesting that either de novo p53 protein synthesis or some proteins synthesis for stabilization of p53 is required for apoptosis. In electrophoretic mobility gel-shift assays, nuclear extracts of cells treated with curcumin displayed distinct patterns of binding between p53 and its consensus binding site. Supportive of these findings, p53 downstream targets, including p21(CIP1/WAF1) and Gadd45, could be induced to localize on the nucleus by curcumin with similar p53 kinetics. Moreover, we immunoprecipitated extracts from basal cell carcinoma cells with different anti-p53 antibodies, which are known to be specific for wild-type or mutant p53 protein. The results reveal that basal cell carcinoma cells contain exclusively wild-type p53; however, curcumin treatment did not interfere with cell cycling. Similarly, the apoptosis suppressor Bcl-2 and promoter Bax were not changed with the curcumin treatment. Finally, treatment of cells with p53 antisense oligonucleotide could effectively prevent curcumin-induced intracellular

p53 protein increase and apoptosis, but sense p53 oligonucleotide could not. Thus, our data suggest that the p53-associated signaling pathway is critically involved in curcumin-mediated apoptotic cell death. This evidence also suggests that curcumin may be a potent agent for skin cancer prevention or therapy.

Se-methylselenocysteine induces apoptosis mediated by reactive oxygen species in HL-60 cells.

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Free Radic Biol Med 2001a Aug 15;31(4):479-89

Recent studies have implicated apoptosis as one of the most plausible mechanisms of the chemopreventive effects of selenium compounds, and reactive oxygen species (ROS) as important mediators in apoptosis induced by various stimuli. In the present study, we demonstrate that Se-methylselenocysteine (MSC), one of the most effective selenium compounds at chemoprevention, induced apoptosis in HL-60 cells and that ROS plays a crucial role in MSC-induced apoptosis. The uptake of MSC by HL-60 cells occurred quite early, reaching the maximum within 1 h. The dose-dependent decrease in cell viability was observed by MSC treatment and was coincident with increased DNA fragmentation and sub-G(1) population. 50 microM of MSC was able to induce apoptosis in 48% of cell population at a 24 h time point. Moreover, the release of cytochrome c from mitochondria and the activation of caspase-3 and caspase-9 were also observed. The measurement of ROS by dichlorofluorescein fluorescence revealed that dose- and time-dependent increase in ROS was induced by MSC. N-acetylcysteine, glutathione, and deferoxamine blocked cell death, DNA fragmentation, and ROS generation induced by MSC. Moreover, N-acetylcysteine effectively blocked caspase-3 activation and the increase of the sub-G(1) population induced by MSC. These results imply that ROS is a critical mediator of the MSC-induced apoptosis in HL-60 cells.

EGCG, a major component of green tea, inhibits tumour growth by inhibiting VEGF induction in human colon carcinoma cells.

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Br J Cancer 2001b Mar 23;84(6):844-50

Catechins are key components of teas that have antiproliferative properties. We investigated the effects of green tea catechins on intracellular signalling and VEGF induction in vitro in serum-deprived HT29 human colon cancer cells and in vivo on the growth of HT29 cells in nude mice. In the in vitro studies, (-)-epigallocatechin gallate (EGCG), the most abundant catechin in green tea extract, inhibited Erk-1 and Erk-2 activation in a dose-dependent manner. However, other

tea catechins such as (-)-epigallocatechin (EGC), (-)-epicatechin gallate (ECG), and (-)-epicatechin (EC) did not affect Erk-1 or 2 activation at a concentration of 30 microM. EGCG also inhibited the increase of VEGF expression and promoter activity induced by serum starvation. In the in vivo studies, athymic BALB/c nude mice were inoculated subcutaneously with HT29 cells and treated with daily intraperitoneal injections of EC (negative control) or EGCG at 1.5 mg day⁻¹ mouse⁻¹ starting 2 days after tumour cell inoculation. Treatment with EGCG inhibited tumour growth (58%), microvessel density (30%), and tumour cell proliferation (27%) and increased tumour cell apoptosis (1.9-fold) and endothelial cell apoptosis (3-fold) relative to the control condition (P< 0.05 for all comparisons). EGCG may exert at least part of its anticancer effect by inhibiting angiogenesis through blocking the induction of VEGF. Copyright 2001 Cancer Research Campaign.

Progress on therapy of breast cancer with vitamin Q10 and the regression of metastases.

Lockwood K, Moesgaard S, Yamamoto T, Folkers K. Pharma Nord, Vejle, Denmark.

Biochem Biophys Res Commun 1995 Jul 6;212(1):172-7

Over 35 years, data and knowledge have internationally evolved from biochemical, biomedical and clinical research on vitamin Q10 (coenzyme Q10; CoQ10) and cancer, which led in 1993 to overt complete regression of the tumors in two cases of breast cancer. Continuing this research, three additional breast cancer patients also underwent a conventional protocol of therapy which included a daily oral dosage of 390 mg of vitamin Q10 (Bio-Quinone of Pharma Nord) during the complete trials over 3-5 years. The numerous metastases in the liver of a 44-year-old patient "disappeared," and no signs of metastases were found elsewhere. A 49-year-old patient, on a dosage of 390 mg of vitamin Q10, revealed no signs of tumor in the pleural cavity after six months, and her condition was excellent. A 75-year-old patient with carcinoma in one breast, after lumpectomy and 390 mg of CoQ10, showed no cancer in the tumor bed or metastases. Control blood levels of CoQ10 of 0.83-0.97 and of 0.62 micrograms/ml increased to 3.34-3.64 and to 3.77 micrograms/ml, respectively, on therapy with CoQ10 for patients A-MRH and EEL.

Protection against anthramycin-induced toxicity in mice by coenzyme Q10.

Lubawy WC, Dallam RA, Hurley LH.

J Natl Cancer Inst 1980 Jan;64(1):105-9

Pretreatment of Swiss Webster mice with coenzyme Q10 (CoQ) markedly reduced the lethality of the antitumor antibiotic anthramycin as well as its ability to decrease ventricular weights. In tumor-bearing mice CoQ pretreatment did not produce any consistent alteration of radioactivity levels in blood, heart, tumor, lungs, kidneys, liver, muscles, brain, or spleen after [^{15-3H}]anthramycin

administration. Gross alterations in anthramycin distribution is probably not the mechanism by which CoQ alters the cardiotoxicity and lethality of anthramycin.

Diet and the risk of breast cancer in a case-control study: does the threat of disease have an influence on recall bias?

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J Clin Epidemiol 1999 May;52(5):429-39

It has been suggested that recall bias may explain the discrepant results between case-control and cohort studies on diet and the risk of breast cancer. Two control groups were used for this case-control study of 25 to 75-year-old breast cancer cases (n = 310). The first group consisted of population controls drawn from the Finnish National Population Register (n = 454). The second group consisted of women who were referred to the same examinations as were the cases because of clinical suspicion of breast disease but who were later diagnosed as healthy (referral controls; n = 506). Because the diagnosis was unknown at the time of interview, it was possible to assess by comparing the two control groups whether the self-reporting of diet changed under the threat of disease. Dietary habits were examined using a validated, self-administered food-frequency questionnaire. Premenopausal women misreported their consumption of liquid milk products, tea, and sugar. Reporting bias was also associated with the intake of fat and vitamins. Postmenopausal women misreported consumption of milk products. When recall bias was taken into consideration, milk was associated with increased risk of premenopausal breast cancer, whereas high consumption of poultry or high intake of monounsaturated fatty acids, n-3 fatty acids, n-6 fatty acids, and vitamin E were related to lower risk. The study suggested that oil, milk, cheese, coffee and beta-carotene may act as protective factors in postmenopausal women, whereas butter and cream may be risk factors for breast cancer. In summary, it is possible that some food items may be overreported or underreported under the threat of disease in health-conscious population. However, most of the results in this study were not modified by recall bias.

Activation of PPARgamma may mediate a portion of the anticancer activity of conjugated linoleic acid.

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Med Hypotheses 2000 Sep;55(3):187-8

A number of human cancer cell lines express the PPARgamma transcription factor, and agonists for PPARgamma are reported to promote apoptosis in these cell lines and impede their clonal expansion both in vitro and in vivo. Conjugated linoleic acid (CLA) can activate PPARgamma in rat adipocytes, possibly explaining CLA's antidiabetic effects in Zucker fatty rats. It is thus reasonable to suspect that a portion of CLA's broad spectrum anticarcinogenic activity is mediated by PPARgamma activation in susceptible tumors.

Antiproliferative and apoptotic effects of tocopherols and tocotrienols on preneoplastic and neoplastic mouse mammary epithelial cells.

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Proc Soc Exp Biol Med 2000 Sep;224(4):292-301

Studies were conducted to determine the comparative effects of tocopherols and tocotrienols on preneoplastic (CL-S1), neoplastic (-SA), and highly malignant (+SA) mouse mammary epithelial cell growth and viability in vitro. Over a 5-day culture period, treatment with 0-120 microM alpha- and gamma-tocopherol had no effect on cell proliferation, whereas growth was inhibited 50% (IC50) as compared with controls by treatment with the following: 13, 7, and 6 microM tocotrienol-rich-fraction of palm oil (TRF); 55, 47, and 23 microM delta-tocopherol; 12, 7, and 5 microM alpha-tocotrienol; 8, 5, and 4 microM gamma-tocotrienol; or 7, 4, and 3 microM delta-tocotrienol in CL-S1, -SA and +SA cells, respectively. Acute 24-hr exposure to 0-250 microM alpha- or gamma-tocopherol (CL-S1, -SA, and +SA) or 0-250 microM delta-tocopherol (CL-S1) had no effect on cell viability, whereas cell viability was reduced 50% (LD50) as compared with controls by treatment with 166 or 125 microM delta-tocopherol in -SA and +SA cells, respectively. Additional LD50 doses were determined as the following: 50, 43, and 38 microM TRF; 27, 28, and 23 microM alpha-tocotrienol; 19, 17, and 14 microM gamma-tocotrienol; or 16, 15, or 12 microM delta-tocotrienol in CL-S1, -SA, and +SA cells, respectively. Treatment-induced cell death resulted from activation of apoptosis, as indicated by DNA fragmentation. Results also showed that CL-S1, -SA, and +SA cells preferentially accumulate tocotrienols as compared with tocopherols, and this may partially explain why tocotrienols display greater biopotency than tocopherols. These data also showed that highly malignant +SA cells were the most sensitive, whereas the preneoplastic CL-S1 cells were the least sensitive to the antiproliferative and apoptotic effects of tocotrienols, and suggest that tocotrienols may have potential health benefits in preventing and/or reducing the risk of breast cancer in women.

Changes in levels of urinary estrogen metabolites after oral indole-3-carbinol treatment in humans.

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J Natl Cancer Inst 1997 May 21;89(10):718-23

BACKGROUND: The oxidative metabolism of estrogens in humans is mediated primarily by cytochrome P450, many isoenzymes of which are inducible by dietary and pharmacologic agents. One major pathway, 2-hydroxylation, is induced by dietary indole-3-carbinol (I3C), which is present in cruciferous vegetables (e.g., cabbage and broccoli).

PURPOSE: Because the pool of available estrogen substrates for all pathways is limited, we hypothesized that increased 2-hydroxylation of estrogens would lead to decreased activity in competing metabolic pathways.

METHODS: Urine samples were collected from subjects before and after oral ingestion of I3C (6-7 mg/kg per day). In the first study, seven men received I3C for 1 week; in the second study, 10 women received I3C for 2 months. A profile of 13 estrogens was measured in each sample by gas chromatography-mass spectrometry.

RESULTS: In both men and women, I3C significantly increased the urinary excretion of C-2 estrogens. The urinary concentrations of nearly all other estrogen metabolites, including levels of estradiol, estrone, estriol, and 16 α -hydroxyestrone, were lower after I3C treatment.

CONCLUSIONS: These findings support the hypothesis that I3C-induced estrogen 2-hydroxylation results in decreased concentrations of several metabolites known to activate the estrogen receptor. This effect may lower estrogenic stimulation in women.

IMPLICATIONS: I3C may have chemopreventive activity against breast cancer in humans, although the long-term effects of higher catechol estrogen levels in women require further investigation.

Altered estrogen metabolism and excretion in humans following consumption of indole-3-carbinol.

Michnovicz JJ, Bradlow HL. Institute for Hormone Research, New York, NY 10016.

Nutr Cancer 1991;16(1):59-66

Research studies have demonstrated a strong association between estrogen metabolism and the incidence of breast cancer, and we have therefore sought pharmacological means of favorably altering both metabolism and subsequent risk. Indole-3-carbinol (I3C), obtained from cruciferous vegetables (e.g., cabbage, broccoli, etc.), is a known inducer of oxidative P-450 metabolism in animals. We investigated the effects in humans of short-term oral exposure to this compound (6-7 mg/kg/day over 7 days). We used an in vivo radiometric test, which provided a highly specific and reproducible measure of estradiol 2-hydroxylation before and after exposure to I3C. In a group of 12 healthy volunteers, the average extent of reaction increased by approximately 50% during this short exposure (p less than 0.01), affecting men and women equally. We also measured the urinary excretion of two key estrogen metabolites, 2-hydroxyestrone (2OHE1) and estriol (E3). We found that the excretion of 2OHE1 relative to that of E3 was significantly increased by I3C, further confirming the ongoing induction of 2-hydroxylation. These results indicate that I3C predictably alters endogenous estrogen metabolism toward increased catechol estrogen production and may thereby provide a novel "dietary" means for reducing cancer risk.

Tocotrienols inhibit growth of ZR-75-1 breast cancer cells.

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Int J Food Sci Nutr 2000;51 Suppl:S95-103

The vitamin E component of palm oil provides a rich source of tocotrienols which have been shown previously to be growth inhibitory to two human breast cancer cell lines: responsive MCF7 cells and unresponsive MDA-MB-231 cells. Data presented here shows that the tocotrienol-rich fraction (TRF) of palm oil and individual fractions (alpha, gamma and delta) can also inhibit the growth of another responsive human breast cancer cell line, ZR-75-1. At low concentrations in the absence of oestrogen tocotrienols stimulated growth of the ZR-75-1 cells, but at higher concentrations in the presence as well as in the absence of oestradiol, tocotrienols inhibited cell growth strongly. As for MCF7 cells, alpha-tocopherol had no effect on growth of the ZR-75-1 cells in either the absence or presence of oestradiol. In studying the effects of tocotrienols in combination with antioestrogens, it was found that TRF could further inhibit growth of ZR-75-1 cells in the presence of tamoxifen (10^{-7} M and 10^{-8} M). Individual tocotrienol fractions (alpha, gamma, delta) could inhibit growth of ZR-75-1 cells in the presence of 10^{-8} M oestradiol and 10^{-8} M pure antioestrogen ICI 164,384. The immature mouse uterine weight bioassay confirmed that TRF could not exert oestrogen antagonist action in vivo. These results provide evidence of wider growth-inhibitory effects of tocotrienols beyond MCF7 and MDA-MB-231 cells, and with an oestrogen-independent mechanism of action, suggest a possible clinical advantage in combining administration of tocotrienols with antioestrogen therapy.

Tocotrienols inhibit the growth of human breast cancer cells irrespective of estrogen receptor status.

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Lipids 1998 May;33(5):461-9

Potential antiproliferative effects of tocotrienols, the major vitamin E component in palm oil, were investigated on the growth of both estrogen-responsive (ER+) MCF7 human breast cancer cells and estrogen-unresponsive (ER-) MDA-MB-231 human breast cancer cells, and effects were compared with those of alpha-tocopherol (alphaT). The tocotrienol-rich fraction (TRF) of palm oil inhibited growth of MCF7 cells in both the presence and absence of estradiol with a nonlinear dose-response but such that complete suppression of growth was achieved at 8 microg/mL. MDA-MB-231 cells were also inhibited by TRF but with a linear dose-response such that 20 microg/mL TRF was needed for complete growth suppression. Separation of the TRF into individual tocotrienols revealed that all fractions could inhibit growth of both ER+ and ER- cells and of

ER+ cells in both the presence and absence of estradiol. However, the gamma- and delta-fractions were the most inhibitory. Complete inhibition of MCF7 cell growth was achieved at 6 microg/mL of gamma-tocotrienol/delta-tocotrienol (gammaT3/deltaT3) in the absence of estradiol and 10 microg/mL of deltaT3 in the presence of estradiol, whereas complete suppression of MDA-MB-231 cell growth was not achieved even at concentrations of 10 microg/mL of deltaT3. By contrast to these inhibitory effects of tocotrienols, alphaT had no inhibitory effect on MCF7 cell growth in either the presence or the absence of estradiol, nor on MDA-MB-231 cell growth. These results confirm studies using other sublines of human breast cancer cells and demonstrate that tocotrienols can exert direct inhibitory effects on the growth of breast cancer cells. In searching for the mechanism of inhibition, studies of the effects of TRF on estrogen-regulated pS2 gene expression in MCF7 cells showed that tocotrienols do not act via an estrogen receptor-mediated pathway and must therefore act differently from estrogen antagonists. Furthermore, tocotrienols did not increase levels of growth-inhibitory insulin-like growth factor binding proteins (IGFBP) in MCF7 cells, implying also a different mechanism from that proposed for retinoic acid inhibition of estrogen-responsive breast cancer cell growth. Inhibition of the growth of breast cancer cells by tocotrienols could have important clinical implications not only because tocotrienols are able to inhibit the growth of both ER+ and ER- phenotypes but also because ER+ cells could be growth-inhibited in the presence as well as in the absence of estradiol. Future clinical applications of TRF could come from potential growth suppression of ER+ breast cancer cells otherwise resistant to growth inhibition by antiestrogens and retinoic acid.

Melatonin and steroid-dependent carcinomas.

Oosthuizen JM, Bornman MS, Barnard HC, Schulenburg GW, Boomker D, Reif S. Department of Physiology, University of the Orange Free State, Bloemfontein, South Africa.

Andrologia 1989 Sep-Oct;21(5):429-31

In this study the concentrations of plasma melatonin in patients with either prostatic or breast carcinoma were compared to the levels of controls. The mean melatonin was statistically lower in patients with breast cancer as compared to controls (p less than 0.005). In prostatic carcinoma patients, the mean melatonin was statistically higher than in the control group (p less than 0.005). From the results it would seem that low melatonin levels could possibly play a role in breast carcinoma, but the same did not necessarily apply to prostatic cancer.

Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex.

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Colorectal cancer is a major cause of cancer deaths in Western countries, but epidemiological data suggest that dietary modification might reduce these by as much as 90%. Cyclo-oxygenase 2 (COX2), an inducible isoform of prostaglandin H synthase, which mediates prostaglandin synthesis during inflammation, and which is selectively overexpressed in colon tumours, is thought to play an important role in colon carcinogenesis. Curcumin, a constituent of turmeric, possesses potent anti-inflammatory activity and prevents colon cancer in animal models. However, its mechanism of action is not fully understood. We found that in human colon epithelial cells, curcumin inhibits COX2 induction by the colon tumour promoters, tumour necrosis factor alpha or fcapentaene-12. Induction of COX2 by inflammatory cytokines or hypoxia-induced oxidative stress can be mediated by nuclear factor kappa B (NF-kappaB). Since curcumin inhibits NF-kappaB activation, we examined whether its chemopreventive activity is related to modulation of the signalling pathway which regulates the stability of the NF-kappaB-sequestering protein, IkappaB. Recently components of this pathway, NF-kappaB-inducing kinase and IkappaB kinases, IKKalpha and beta, which phosphorylate IkappaB to release NF-kappaB, have been characterised. Curcumin prevents phosphorylation of IkappaB by inhibiting the activity of the IKKs. This property, together with a long history of consumption without adverse health effects, makes curcumin an important candidate for consideration in colon cancer prevention.

Coenzyme Q10 concentrations and antioxidant status in tissues of breast cancer patients.

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Clin Biochem 2000 Jun;33(4):279-84

OBJECTIVES: An increasing amount of experimental and epidemiological evidence implicates the involvement of oxygen derived radicals in the pathogenesis of cancer development. Oxygen derived radicals are able to cause damage to membranes, mitochondria, and macromolecules including proteins, lipids and DNA. Accumulation of DNA damages has been suggested to contribute to carcinogenesis. It would, therefore, be advantageous to pinpoint the effects of oxygen derived radicals in cancer development.

DESIGN AND METHODS: In the present study, we investigated the relationship between oxidative stress and breast cancer development in tissue level. Breast cancer is the most common malignant disease in Western women. Twenty-one breast cancer patients, who underwent radical mastectomy and diagnosed with infiltrative ductal carcinoma, were used in the study. We determined coenzyme Q10 (Q) concentrations, antioxidant enzyme activities (mitochondrial and total superoxide dismutase (SOD), glutathione peroxidase (GSH-Px), catalase), and malondialdehyde (MDA) levels in tumor and surrounding tumor-free tissues.

RESULTS: Q concentrations in tumor tissues significantly decreased as compared to the surrounding normal tissues ($p < 0.001$). Higher MDA levels were observed in tumor tissues than noncancerous tissues ($p < 0.001$). The activities of MnSOD, total SOD, GSH-Px and catalase in tumor tissues significantly increased ($p < 0.001$) compared to the controls.

CONCLUSIONS: These findings may support that reactive oxygen species increased in malignant cells, and may cause overexpression of antioxidant enzymes and the consumption of coenzyme Q10. Increased antioxidant enzyme activities may be related with the susceptibility of cells to carcinogenic agents and the response of tumor cells to the chemotherapeutic agents. Administration of coenzyme Q10 by nutrition may induce the protective effect of coenzyme Q10 on breast tissue.

Curcumin is a non-competitive and selective inhibitor of phosphorylase kinase.

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FEBS Lett 1994 Mar 14;341(1):19-22

Recently, we reported that curcumin (diferuloylmethane) inhibits the growth of several different kinds of tumor cells. In order to investigate the mechanism of this inhibition, we examined the effects of curcumin on different protein kinases: highly purified protein kinase A (Pka), protein kinase C (Pkc), protamine kinase (cPK), phosphorylase kinase (PhK), autophosphorylation-activated protein kinase (AK) and pp60c-src tyrosine kinase. While all kinases tested were inhibited by curcumin, only PhK was completely inhibited at relatively lower concentrations. At around 0.1 mM curcumin, PhK, pp60c-src, Pkc, Pka, AK, and cPK were inhibited by 98%, 40%, 15%, 10%, 1%, and 0.5%, respectively. Lineweaver-Burk plot analysis indicated that curcumin is a non-competitive inhibitor of PhK with a K_i of 0.075 mM. Overall, our results indicate that curcumin is a potent and selective inhibitor of phosphorylase kinase, a key regulatory enzyme involved in the metabolism of glycogen. This has important implications for the anti-proliferative effects of curcumin.

Natural products and their derivatives as cancer chemopreventive agents.

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Prog Drug Res 1997;48:147-71

This review summarizes currently available data on the chemopreventive efficacies, proposed mechanisms of action and relationships between activities and structures of natural products like vitamin D, calcium, dehydroepidandrosterone, coenzyme Q10, celery seed oil, parsley leaf oil,

sulforaphane, isoflavonoids, lignans, protease inhibitors, tea polyphenols, curcumin, and polysaccharides from *Acanthopanax* genus.

Serum fatty acid imbalance in bone loss: example with periodontal disease.

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Clin Nutr 2000 Aug;19(4):271-6

Among the numerous factors of bone remodelling, the local action of arachidonic acid metabolites together with cytokines, is particularly important, especially that of prostaglandin PGE₂. It has been suggested that the alveolar bone destruction in periodontal disease and osteoporosis can be treated by reducing the ratio of arachidonic acid in phospholipids, which would diminish prostaglandin production. The aim of this study was to evaluate the main serum polyunsaturated fatty acids and a possible alteration in the level of arachidonic acid in patients suffering from periodontal bone loss. Of the 105 patients who participated the study, 78 were suffering from periodontal bone loss and 27 served as a control group. The fatty acids were measured in serum by gas-chromatography. The results showed that the level of fatty acids of the n-6 pathway was higher in our patients with bone loss than in the control group, whereas the reverse was observed with fatty acids of the n-3 pathway. In conclusion, our patients' bone losses are linked with an imbalance between n-6 and n-3 fatty acids, which seems to justify a diet increase in 20- and 22-carbon fatty acids. Copyright 2000 Harcourt Publishers Ltd.

Free radical recycling and intramembrane mobility in the antioxidant properties of alpha-tocopherol and alpha-tocotrienol.

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Free Radic Biol Med 1991;10(5):263-75

d-Alpha-tocopherol (2R,4'R,8'R-Alpha-tocopherol) and d-alpha-tocotrienol are two vitamin E constituents having the same aromatic chromanol "head" but differing in their hydrocarbon "tail": tocopherol with a saturated and toctrienol with an unsaturated isoprenoid chain. d-Alpha-tocopherol has the highest vitamin E activity, while d-alpha-tocotrienol manifests only about 30% of this activity. Since vitamin E is considered to be physiologically the most important lipid-soluble chain-breaking antioxidant of membranes, we studied alpha-tocotrienol as compared to alpha-tocopherol under conditions which are important for their antioxidant function. d-Alpha-tocotrienol possesses 40-60 times higher antioxidant activity against (Fe²⁺ + ascorbate)- and (Fe²⁺ + NADPH)-induced lipid peroxidation in rat liver microsomal membranes and 6.5 times better protection of cytochrome P-450 against oxidative damage than d-alpha-tocopherol. To clarify the mechanisms responsible for the much higher antioxidant potency of d-alpha-tocotrienol compared to d-alpha-tocopherol, ESR

studies were performed of recycling efficiency of the chromanols from their chromanoxyl radicals. ¹H-NMR measurements of lipid molecular mobility in liposomes containing chromanols, and fluorescence measurements which reveal the uniformity of distribution (clusterizations) of chromanols in the lipid bilayer. From the results, we concluded that this higher antioxidant potency of d-alpha-tocotrienol is due to the combined effects of three properties exhibited by d-alpha-tocotrienol as compared to d-alpha-tocopherol: (i) its higher recycling efficiency from chromanoxyl radicals, (ii) its more uniform distribution in membrane bilayer, and (iii) its stronger disordering of membrane lipids which makes interaction of chromanols with lipid radicals more efficient. The data presented show that there is a considerable discrepancy between the relative in vitro antioxidant activity of d-alpha-tocopherol and d-alpha-tocotrienol with the conventional bioassays of their vitamin activity.

Intervention in free radical mediated hepatotoxicity and lipid peroxidation by indole-3-carbinol.

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Biochem Pharmacol 1988 Jan 15;37(2):333-8

The cytoprotective effect of the natural dietary constituent indole-3-carbinol (I-3-C) on carbon tetrachloride (CCl₄) mediated hepatotoxicity in mice was examined. I-3-C pretreatment by gavage 1 hr prior to intraperitoneal injection of CCl₄ produced a 63% decrease in CCl₄-mediated centrilobular necrosis and a related 60% decrease in plasma alanine aminotransferase activity (a marker of liver necrosis). Since the toxicological effects of CCl₄ are mediated by radical species generated during reductive metabolism by cytochrome P-450, we examined the potential ability of I-3-C to scavenge reactive radicals. Three systems were used to evaluate the ability of I-3-C to intervene in free radical mediated lipid peroxidation. These systems consisted of the following: (1) phospholipid dissolved in chlorobenzene, with peroxidation initiated by the thermal and photo decomposition of azobisisobutyronitrile (AIBN); (2) sonicated phospholipid vesicles in phosphate buffer (pH 7.4), with peroxidation initiated by ferrous/ascorbate; and (3) mouse liver microsomes containing an NADPH-regenerating system, with peroxidation initiated with CCl₄. Lipid peroxidation was measured in these three systems as thiobarbiturate-reacting material. In the AIBN and ferrous/ascorbate systems, I-3-C inhibited lipid peroxidation, with greater inhibition under conditions of low rates of free radical generation. I-3-C was not as effective an antioxidant as butylated hydroxytoluene (BHT) or tocopherol, but it inhibited peroxidation in a dose-response manner. I-3-C was most effective as a radical scavenger in the microsomal CCl₄-initiated system by inhibiting lipid peroxidation in a dose-dependent fashion, with 50% inhibition at 35-40 microM I-3-C. This concentration is about one-third of the concentration of I-3-C achieved in liver after treatment of mice by gavage with 50 mg I-3-C/kg body weight. These data suggest that I-3-C may be a natural antioxidant in the human diet and, as such, may intervene in toxicological or carcinogenic processes that are mediated by radical mechanisms.

Enhancement of wound healing by curcumin in animals.

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Wound Repair Regen 1998 Mar-Apr;6(2):167-77

Tissue repair and wound healing are complex processes that involve inflammation, granulation, and remodeling of the tissue. In this study, we evaluated the in vivo effects of curcumin (diferuloylmethane), a natural product obtained from the rhizomes of *Curcuma longa* on wound healing in rats and guinea pigs. We observed faster wound closure of punch wounds in curcumin-treated animals in comparison with untreated controls. Biopsies of the wound showed reepithelialization of the epidermis and increased migration of various cells including myofibroblasts, fibroblasts, and macrophages in the wound bed. Multiple areas within the dermis showed extensive neovascularization, and Masson's Trichrome staining showed greater collagen deposition in curcumin-treated wounds. Immunohistochemical localization of transforming growth factor-beta1 showed an increase in curcumin-treated wounds as compared with untreated wounds. In situ hybridization and polymerase chain reaction analysis also showed an increase in the mRNA transcripts of transforming growth factor-beta1 and fibronectin in curcumin-treated wounds. Because transforming growth factor-beta1 is known to enhance wound healing, it may be possible that transforming growth factor-beta1 plays an important role in the enhancement of wound healing by curcumin.

Effects of methylselenocysteine on PKC activity, cdk2 phosphorylation and gadd gene expression in synchronized mouse mammary epithelial tumor cells.

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Cancer Lett 1999 Nov 15;146(2):135-45

Methylselenocysteine (MSC), an organic selenium compound is an effective chemopreventive agent against mammary cell growth both in vivo and in vitro but its mechanism of action is still not understood. We have previously demonstrated that MSC is able to inhibit growth in a synchronized TM6 mouse mammary epithelial tumor cell line at 16 h time point followed by apoptosis at 48 h. The decrease in cdk2 kinase activity was coincident with prolonged arrest of cells in S-phase. The present set of experiments showed that cdk2 phosphorylation was reduced by 72% in the MSC-treated cells at 16 h time point. Expression for gadd34, 45 and 153 was elevated 2.5 to 7 fold following MSC treatment only after 16 h time point. In order to investigate a possible upstream target for MSC, we analyzed protein kinase C (PKC) in this model. Total PKC activity was

reduced in TM6 cells by MSC (50 microM) within 30 min of treatment, both in cytosolic (55.4 and 77.6%) and membrane (35.2 and 34.1%) fractions for calcium-dependent and independent PKCs, respectively. PMA significantly elevated the PKC activity in membrane fraction ($P < 0.01$) and MSC inhibited this activation by more than 57%. The effect of MSC was selenium specific as selenomethionine and sulfurmethyl-L-cysteine (SMC) did not alter PKC activity either in cytosolic or membrane fraction. Immunoblot analysis showed that PKC-alpha was translocated to the membrane by PMA and MSC did not alter this translocation. PKC-delta was faintly detectable in membrane fractions of control and MSC-treated cells. MSC treatment slightly reduced levels of PKC-e (in cytosolic and membrane fractions) and PKC-zeta (cytosolic fractions). The data presented herein suggest that PKC is a potential upstream target for MSC that may trigger one or all of the downstream effects; i.e. the decrease of cdk2 kinase activity, decreased DNA synthesis, elevation of gadd gene expression and finally apoptosis.

Inhibition of cdk2 kinase activity by methylselenocysteine in synchronized mouse mammary epithelial tumor cells.

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Carcinogenesis 1997 Aug;18(8):1541-7

Methylselenocysteine (MSC), an organic selenium compound has significant anticarcinogenic activity against mammary tumorigenesis. Previous experiments have demonstrated that MSC and inorganic selenite inhibit mammary cell (TM6 cell line) growth through different pathways. The present investigation demonstrated that MSC arrested cells in S phase during the TM6 cell cycle, which was followed by cells entering apoptosis at 48 h. Methylselenocysteine specifically affected the cdk2 kinase activity of the TM6 cells (54% reduction) at 16 h after release from growth arrest. The cdk4 kinase activity did not change during the cell cycle, confirming that cells had passed the G1 checkpoint and had entered S phase. The amount of cyclin E associated with cdk2 was increased by MSC by the 12 h time point, thereby facilitating entry of cells into S phase. Afterwards, cyclin E and cyclin A associated with cdk2 did not change for the remainder of the cell cycle. The data demonstrate that inhibition of mammary cell growth by MSC is mediated by alterations in progression of cells through S phase. The decrease in cdk2 kinase activity is coincident with prolonged arrest in S phase. One consequence of prolonged arrest may be apoptosis.

Effect of dietary palm oils on mammary carcinogenesis in female rats induced by 7,12-dimethylbenz(a)anthracene.

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Cancer Res 1989 Mar 15;49(6):1447-51

Female Sprague-Dawley rats, 50 days of age, were treated with a single dose of 5 mg of 7,12-dimethylbenz(a)anthracene intragastrically. 3 days after carcinogen treatment, the rats were put on semisynthetic diets containing 20% by weight of corn oil (CO), soybean oil (SBO), crude palm oil (CPO), refined, bleached, deodorized palm oil (RBD PO) and metabisulfite-treated palm oil (MCPO) for 5 months. During the course of experiments, rats fed on different dietary fats had similar rate of growth. Rats fed 20% CO or SBO diet have higher tumor incidence than rats fed on palm oil (PO) diets; however differences of mean tumor latency periods among the groups were not statistically significant. At autopsy, rats fed on high CO or SBO diets had significantly more tumors than rats fed on the three PO diets. Our results showed that high PO diets did not promote chemically induced mammary tumorigenesis in female rats when compared to high CO or SBO diets. CO and SBO differ greatly from the palm oils in their contents of tocopherols, tocotrienols, and carotenes. But further experiments would be required to determine whether the observed differences in tumor incidence and tumor numbers were due to the differences in these minor components or due to the unique triglyceride structure of the palm oils. Analysis of the fatty acid profiles of plasma total lipids of tumor-bearing rats and of the tumor total lipids showed that, with the exception of arachidonic acid, the fatty acid profiles reflect the nature of the dietary fats. At autopsy, there were no differences in the plasma total cholesterol contents among rats fed on different dietary fats, but rats fed on palm oil diets had a significantly higher plasma triglyceride level than that of rats fed CO or SBO diets. As for the tumor lipids, there were no significant differences in the triglyceride, diglyceride, and phospholipid levels when the CO or SBO groups were compared to the palm oil groups.

Inhibition of proliferation and modulation of estradiol metabolism: novel mechanisms for breast cancer prevention by the phytochemical indole-3-carbinol.

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Proc Soc Exp Biol Med 1997 Nov;216(2):246-52

Aberrant proliferation is an early-occurring intermediate event in carcinogenesis whose inhibition may represent preventive intervention. Indole-3-carbinol (I3C), a glucosinolate metabolite from cruciferous vegetables, inhibits organ site carcinogenesis in rodent models. Clinically relevant biochemical and cellular mechanisms for the anticarcinogenic effects of I3C, however, remain unclear. Experiments were conducted on reduction mammoplasty derived 184-B5 cells initiated with chemical carcinogen (184-B5/BP) or with oncogene (184-B5/HER), and on mammary-carcinoma-derived MDA-MD-231 cells to examine whether (i) I3C inhibits aberrant proliferation in initiated and transformed cells, and (ii) inhibition of aberrant proliferation is associated with altered cell-cycle progression, estradiol (E2) metabolism, and apoptosis. Aberrant proliferation in 184-B5/BP, 184-B5/HER, and MDA-MB-231 cells was evident by a 55%-67% decrease in the ratio of quiescent (Q = G₀) to proliferative (P = S + M) phase of

the cell cycle, a 72%-90% decrease in apoptosis, and a 76%-106% increase in anchorage-dependent growth. These cells also exhibited a 88%-90% decrease in the ratio of C2 to C16alpha-hydroxylation products of E2. Treatment of 184-B5/BP, 184-B5/HER, and MDA-MB-231 cells to cytostatic dose of 50 microM I3C resulted in an 137%-210% increase in Q/P I3C ratio, a 4- to 18-fold increase in E2 metabolite ratio, a 2-fold increase in cellular apoptosis, and a 54%-61% inhibition of growth. The preventive efficacy of I3C on human mammary carcinogenesis may be due in part to its ability to regulate cell-cycle progression, increase the formation of antiproliferative E2 metabolite, and induce cellular apoptosis.

Tocotrienol: a review of its therapeutic potential.

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Clin Biochem 1999 Jul;32(5):309-19

OBJECTIVES: To summarize new knowledge surrounding the physiological activity of tocotrienol, a natural analogue of tocopherol.

RESULTS: The biological activity of vitamin E has generally been associated with its well-defined antioxidant property, specifically against lipid peroxidation in biological membranes. In the vitamin E group, alpha-tocopherol is considered to be the most active form. However, recent research has suggested tocotrienol to be a better antioxidant. Moreover, tocotrienol has been shown to possess novel hypocholesterolemic effects together with an ability to reduce the atherogenic apolipoprotein B and lipoprotein(a) plasma levels. In addition, tocotrienol has been suggested to have an anti-thrombotic and anti-tumor effect indicating that tocotrienol may serve as an effective agent in the prevention and/or treatment of cardiovascular disease and cancer.

CONCLUSION: The physiological activities of tocotrienol suggest it to be superior than alpha-tocopherol in many situations. Hence, the role of tocotrienol in the prevention of cardiovascular disease and cancer may have significant clinical implications. Additional studies on its mechanism of action, as well as, long-term intervention studies, are needed to clarify its function. From the pharmacological point-of-view, the current formulation of vitamin E supplements, which is comprised mainly of alpha-tocopherol, may be questionable

Possible prevention from the progression of cardiotoxicity in adriamycin-treated rabbits by coenzyme Q10.

Usui T, Ishikura H, Izumi Y, Konishi H, Dohmae N, Sawada H, Uchino H, Matsuda H, Konishi T.

Toxicol Lett 1982 Jun;12(1):75-82

The cumulative dose-dependent cardiotoxicity induced by doxorubicin (adriamycin, ADR) and its possible prevention by coenzyme Q10 (CoQ10) were studied in rabbits. In the group that received ADR alone, ADR dose-dependent electrocardiography (ECG) abnormalities and severe myocardial damage on electron microscopic examination were observed. In the group that received ADR + CoQ10, these alterations occurred in lesser degree, and ECG changes seemed to be improved. The results indicated that CoQ10 might prevent the progression of cardiotoxicity in ADR treated rabbits.

Induction of apoptosis in human breast cancer cells by tocopherols and tocotrienols.

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Nutr Cancer 1999;33(1):26-32

The apoptosis-inducing properties of RRR-alpha-, beta-, gamma-, and delta-tocopherols, alpha-, gamma-, and delta-tocotrienols, RRR-alpha-tocopheryl acetate (vitamin E acetate), and RRR-alpha-tocopheryl succinate (vitamin E succinate) were investigated in estrogen-responsive MCF7 and estrogen-nonresponsive MDA-MB-435 human breast cancer cell lines in culture. Apoptosis was characterized by two criteria: 1) morphology of 4,6-diamidino-2-phenylindole-stained cells and oligonucleosomal DNA laddering. Vitamin E succinate, a known inducer of apoptosis in several cell lines, including human breast cancer cells, served as a positive control. The estrogen-responsive MCF7 cells were more susceptible than the estrogen-nonresponsive MDA-MB-435 cells, with concentrations for half-maximal response for tocotrienols (alpha, gamma, and delta) and RRR-delta-tocopherol of 14, 15, 7, and 97 micrograms/ml, respectively. The tocotrienols (alpha, gamma, and delta) and RRR-delta-tocopherol induced MDA-MB-435 cells to undergo apoptosis, with concentrations for half-maximal response of 176, 28, 13, and 145 micrograms/ml, respectively. With the exception of RRR-delta-tocopherol, the tocopherols (alpha, beta, and gamma) and the acetate derivative of RRR-alpha-tocopherol (RRR-alpha-tocopheryl acetate) were ineffective in induction of apoptosis in both cell lines when tested within the range of their solubility, i.e., 10-200 micrograms/ml. In summary, these studies demonstrate that naturally occurring tocotrienols and RRR-delta-tocopherol are effective apoptotic inducers for human breast cancer cells.

Curcumin inhibits cyclooxygenase-2 transcription in bile acid- and phorbol ester-treated human gastrointestinal epithelial cells.

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Carcinogenesis 1999 Mar;20(3):445-51

We investigated whether curcumin, a chemopreventive agent, inhibited chenodeoxycholate (CD)- or phorbol ester (PMA)-mediated induction of cyclooxygenase-2 (COX-2) in several gastrointestinal cell lines (SK-GT-4, SCC450, IEC-18 and HCA-7). Treatment with curcumin suppressed CD- and PMA-mediated induction of COX-2 protein and synthesis of prostaglandin E₂. Curcumin also suppressed the induction of COX-2 mRNA by CD and PMA. Nuclear run-offs revealed increased rates of COX-2 transcription after treatment with CD or PMA and these effects were inhibited by curcumin. Treatment with CD or PMA increased binding of AP-1 to DNA. This effect was also blocked by curcumin. In addition to the above effects on gene expression, we found that curcumin directly inhibited the activity of COX-2. These data provide new insights into the anticancer properties of curcumin.

Vitamin E concentration in breast adipose tissue of breast cancer patients (Kuopio, Finland).

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Cancer Causes Control 1996 Nov;7(6):591-5

Previous data on animals and humans suggest that vitamin E may be a protective factor against cancer. A low dietary vitamin E intake has been suggested to increase the risk of breast cancer. We examined the dietary intake and the concentration of vitamin E in breast adipose tissue of women in Kuopio, Finland, diagnosed between 1990 and 1992 with benign breast disease (n = 34) and with breast cancer (n = 32). In postmenopausal women, lower dietary intake (P = 0.006) and a smaller concentration of vitamin E in breast adipose tissue (P = 0.024) were observed in breast cancer patients than in subjects with benign breast disease. Partial correlation showed that the vitamin E concentration in the breast adipose tissue correlated positively with the dietary intake of vitamin E (r = 0.25, P = 0.023), indicating that the vitamin E concentration in breast adipose tissue reflects the dietary intake of vitamin E.

11. Cholesterol reduction

Preventative and curative options include:

Garlic, curcumin, guggulipid, artichoke extract, chitosan, psyllium, guar gum, pectin, green tea, niacin, fish oil, soy protein extract, vitamin E, vitamin C, selenium, policosanol, Co-Enzyme Q10, ginseng, ginkgo biloba, zinc.

Dietary isoflavones reduce plasma cholesterol and atherosclerosis in C57BL/6 mice but not LDL receptor-deficient mice.

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J Nutr (United States) Jun 1998, 128 (6) p954-9

Susceptibility to atherosclerosis is determined by a combination of genetic and environmental factors, including diet. Consumption of diets rich in soy protein has been claimed to protect against the development of atherosclerosis. Potential mechanisms include cholesterol lowering, inhibition of lipoprotein oxidation and inhibition of cell proliferation by soy proteins or isoflavones, such as genistein, that are present in soy. This study was designed to determine whether soy isoflavones confer protection against atherosclerosis in mice and whether they reduce serum cholesterol levels and lipoprotein oxidation. C57BL/6 and LDL receptor-deficient (LDLr-null) mice were fed soy protein-based, high fat diets with isoflavones present (IF+, 20.85 g/100 g protein, 0.027 g/100 g genistein, 0.009 g/100 g daidzein) or diets from which isoflavones, and possibly other components, had been extracted (IF-, 20.0 g/100 g protein, 0.002 g/100 g genistein, 0.001 g/100 g daidzein). Because LDLr-null mice develop extensive atherosclerosis and hypercholesterolemia after minimal time on a high fat diet, they were fed the diets for 6 wk, whereas C57BL/6 mice were fed the diets for 10 wk. Plasma cholesterol levels did not differ between LDLr-null mice fed IF- and those fed IF+, but were 30% lower in C57BL/6 mice fed the IF+ diet than in those fed the IF- diet. Susceptibility of LDL to oxidative modification, measured as the lag phase of conjugated diene formation in LDLr-null mice, was not altered by isoflavone consumption. All LDLr-null mice developed atherosclerosis, and the presence or deficiency of dietary isoflavones did not influence atherosclerotic lesion area. In contrast, atherosclerotic lesion area was significantly reduced in C57BL/6 mice fed IF+ compared with those fed IF-. Thus, this study demonstrates that although the isoflavone-containing diet resulted in a reduction in cholesterol levels in C57BL/6 mice, it had no effect on cholesterol levels or on susceptibility of LDL to oxidative modification in LDLr-null mice. Further, dietary isoflavones did not protect against the development of atherosclerosis in LDLr-null mice but did decrease atherosclerosis in C57BL/6 mice. These findings suggest that soy isoflavones might lower cholesterol levels by increasing LDL receptor activity, and the reduction in cholesterol may offer some protection against atherosclerosis.

Evolution of the health benefits of soy isoflavones

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Proceedings of the Society for Experimental Biology and Medicine (United States), 1998, 217/3 (386-392)

Soy is a unique dietary source of the isoflavones , genistein and daidzein. It has been part of the Southeast Asian diet for nearly five millenia, whereas consumption of soy in the United States and Western Europe has been limited to the 20th century. Heavy consumption of soy in Southeast Asian populations is associated with reduction in the rates of certain cancers and cardiovascular disease. Recent experimental evidence suggests that phytochemicals in soy are responsible for its beneficial effects, which may also include prevention of osteoporosis, a hereditary chronic nose bleed syndrome, and autoimmune diseases. Exposure of soy formula-fed infants to the potential estrogenizing effects of the isoflavones is limited by the first pass effect of the liver following the uptake of isoflavones from the gut. Several mechanisms of action of isoflavones have been proposed-both through estrogen-dependent and estrogen-independent pathways.

Polyphenols produced during red wine ageing.

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Biofactors (Netherlands) 1997, 6 (4) p403-10

Over the past few years, it has been accepted that a moderate red wine consumption is a factor beneficial to human health. Indeed, people of France and Italy, the two major wine-producing European countries, eat a lot of fatty foods but suffer less from fatal heart strokes than people in North-America or in the northern regions of Europe, where wine is not consumed on a regular basis. For a time, ethanol was thought to be the "good" chemical species hiding behind what is known as the "French paradox". Researchers now have turned their investigations towards a family of natural substances called "polyphenols", which are only found in plants and are abundant in grapes . It is well known that these molecules behave as radical scavengers and antioxidants, and it has been demonstrated that they can protect cholesterol in the LDL species from oxidation, a process thought to be at the origin of many fatal heart attacks. However, taken one by one, it remains difficult to demonstrate which are the best polyphenols as far as their antioxidant activities are concerned. The main obstacle in that kind of research is not the design of the chemical and biological tests themselves, but surprisingly enough, the limited access to chemically pure and structurally elucidated

polyphenolic compounds. In this article, particular attention will be paid to polyphenols of red wine made from *Vitis vinifera* cultivars. With respect to the "French paradox", we address the following question: are wine polyphenolic compounds identical to those found in grapes (skin, pulp and seed), or are there biochemical modifications specifically taking place on the native flavonoids when a wine ages? Indeed, structural changes occur during wine conservation, and one of the most studied of those changes concerns red wine colour evolution, called "wine ageing". As a wine ages, it has been demonstrated that the initially present grape pigments slowly turn into new more stable red pigments. That phenomenon goes on for weeks, months and years. Since grape and wine polyphenols are chemically distinct, their antioxidant activities cannot be the same. So, eating grapes might well lead to beneficial effects on human health, due to the variety and sometimes large amounts of their polyphenolic content. However, epidemiological surveys have focused on wines, not on grapes (35 Refs.)

Fats in indian diets and their nutritional and health implications

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Lipids (USA), 1996, 31/3 Suppl. (S287-S291)

To arrive at fat requirements for Indians, the contribution of invisible fat should be determined. Total lipids were extracted from common Indian foods, and their fatty acid compositions were determined. This data and information on intake of various foods were used to estimate the contents of 'invisible' fat and fatty acids in Indian diets. Taking into account World Health Organization (WHO) guidelines and the invisible fat intake of Indians, recommendations were made for lower and upper limits of visible fats. In the rural poor, the 'visible'-fat intakes are much lower than estimated minimum requirements. Therefore, to meet the energy needs of low income groups, particularly young children, visible-fat intakes must be increased to recommended levels. The urban high-income group, however, should reduce dietary fat. Data on intake of various fatty acids in total diet shows that even the recommended lower limit of oil can meet linoleic acid requirements. Intake of alpha-linolenic acid is low, however. Increase in dietary n-3 polyunsaturated fatty acid (PUFA) produces hypolipidemic, anti-inflammatory, and antithrombotic effects. Effects of n-3 PUFA on blood lipids, platelet fatty acid composition, and platelet aggregation were therefore investigated in Indian subjects consuming cereal based diets. Supplementation of fish oils (long-chain n-3 PUFA) as well as the use of rapeseed oil (alpha-linolenic acid) produced beneficial effects. Since the requirements of alpha-linolenic acid and/or long-chain n-3 PUFA are related to linoleic acid intake, use of more than one oil (correct choice) is recommended for providing a balanced intake of various fatty acids. Analysis of Indian food showed that some foods are good sources of alpha-linolenic acid. Regular consumption of these foods can also improve the quality of fat in Indian diets. Nonvegetarians, however, have the choice of eating fish to accomplish this.

The effects of natural dietary fiber from fruit and vegetables with oxalate from spinach on plasma minerals, lipids and other metabolites in men

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Nutr. Res. (USA), 1990, 10/4 (367-378)

Diets high in fiber and oxalate may result in decreased mineral bioavailability. However, increased fiber intake can reduce risk factors for some diseases. Twelve men were fed diets containing 25 g or 5 g of neutral detergent fiber with 450 mg/day of oxalic acid for six weeks each in a crossover design to determine whether plasma minerals and other metabolites would be affected. High dietary oxalate levels were fed throughout the study. The fiber sources were fruit and vegetables or their juices and spinach was the source of oxalate. Five minerals and cholesterol, triglycerides, uric acid, glucose and urea nitrogen (BUN) were measured in fasting plasma and correlated with fecal oxalate, mineral intake and apparent mineral balance. Fiber level had no effect on the plasma constituents. Plasma inorganic phosphorus (P(i)) decreased ($p = 0.002$), while BUN, calcium and copper increased ($p < 0.010$), ($p = 0.004$), ($p = 0.011$) with time. BUN and P(i) changes which occurred may have been related to ingestion of high levels of oxalate for eighty-four days.

Medical nutrition therapy lowers serum cholesterol and saves medication costs in men with hypercholesterolemia.

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J Am Diet Assoc (United States) Aug 1998, 98 (8) p889-94; quiz 895-6

This study was designed to evaluate whether medical nutrition therapy administered by registered dietitians could lead to a beneficial clinical and cost outcome in men with hypercholesterolemia. Ninety-five subjects participating in a cholesterol-lowering drug study took part in an 8-week nutrition intervention program before initiating treatment with a cholesterol-lowering medication. Patient records were reviewed via a retrospective chart review to determine plasma lipid levels at the beginning and end of the program and the number and length of sessions with a dietitian. Complete information was available for 74 subjects aged 60.8 \pm 9.8 years (mean \pm SD). Medical nutrition therapy lowered total serum cholesterol levels 13% ($P < .001$), low-density lipoprotein cholesterol (LDL-C) 15% ($P < .0001$), triglyceride 11% ($P < .05$), and high-density lipoprotein-cholesterol (HDL-C) 4% ($P < .05$). Total dietitian intervention time was 144 \pm 21 minutes (range = 120 to 180 minutes) in 2.8 \pm

0.7 sessions (range = 2 to 4) during 6.81 +/- 0.7 weeks of medical nutrition therapy (range = 6 to 8 weeks). Analysis of covariance was conducted to examine whether mean change in LDL-C differed by number of dietitian visits. Results showed a marginal difference between the number of dietitian visits and change in LDL-C ($f = 2.6$, $P < .084$). However, the magnitude of LDL-C reduction was significantly higher with 4 dietitian visits (180 minutes) than with 2 visits (120 minutes) (21.9% vs 12.1%; $P = .027$). Lipid drug eligibility was obviated in 34 of 67 (51%) subjects per the National Cholesterol Treatment Program guidelines algorithm. The estimated annualized cost savings from the avoidance of lipid medications was \$60,561.68. Therefore, we conclude that 3 or 4 individualized dietitian visits of 50 minutes each over 7 weeks are associated with a significant serum cholesterol reduction and a savings of health care dollars.

Effects of crystalline nicotinic acid-induced hepatic dysfunction on serum low-density lipoprotein cholesterol and lecithin cholesteryl acyl transferase.

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Am J Cardiol (United States) Mar 15 1998, 81 (6) p805-7

Marked lowering of plasma total and low-density lipoprotein cholesterol levels that occur during treatment of dyslipidemia with pharmacologic doses of nicotinic acid result from hepatotoxicity. Therefore, a marked reduction in low-density lipoprotein may suggest generalized liver toxicity and drug treatment should be discontinued.

A randomized trial of the effects of atorvastatin and niacin in patients with combined hyperlipidemia or isolated hypertriglyceridemia. Collaborative Atorvastatin Study Group.

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Am J Med (United States) Feb 1998, 104 (2) p137-43

BACKGROUND: To assess the lipid-lowering effects and safety of atorvastatin and niacin in patients with combined hyperlipidemia or isolated hypertriglyceridemia.

METHODS: We performed a randomized, open-label, parallel-design, active-controlled, study in eight centers in the United States. We enrolled 108 patients with total cholesterol (TC) of $>$ or $=200$ mg/dL, serum triglycerides (TG) $>$ or $=200$ and $<$ or $=800$ mg/dL, and apolipoprotein B (apo B) $>$ or $=110$ mg/dL. Patients were randomly assigned to receive atorvastatin 10 mg once daily ($n=55$)

or immediate-release niacin 1 g three times daily for 12 weeks (n=53). Patients were stratified based on low-density lipoprotein cholesterol (LDL-C): Patients with LDL-C \geq 135 mg/dL were considered to have combined hyperlipidemia and patients with LDL-C $<$ 135 mg/dL were considered to have isolated hypertriglyceridemia. The primary outcome measure was percent change from baseline in LDL-C. Other lipid levels were evaluated as secondary parameters.

RESULTS: Atorvastatin reduced LDL-C 30% and TC 26% from baseline, and increased high-density lipoprotein cholesterol (HDL-C) 4%. Total TG were reduced 17%. Niacin reduced LDL-C 2%, TC 7%, increased HDL-C 25%, and reduced total TG 29% from baseline. There was a significant difference in LDL-C reduction, the primary efficacy parameter, between the two treatment groups ($P < 0.05$, favoring atorvastatin), as well as a significant difference in the improvement in HDL-C ($P < 0.05$, favoring niacin). The effect of atorvastatin was relatively consistent between patients with combined hyperlipidemia and isolated hypertriglyceridemia, whereas there was more variability between these strata in the niacin treatment group. Atorvastatin was better tolerated than niacin.

CONCLUSION: Atorvastatin may allow patients with combined hyperlipidemia to be treated with monotherapy and offers an efficacious and well-tolerated alternative to niacin for the treatment of patients with isolated hypertriglyceridemia.

Use of niacin, statins, and resins in patients with combined hyperlipidemia.

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Am J Cardiol (United States) Feb 26 1998, 81 (4A) p52B-59B

Patients in the original Familial Atherosclerosis Treatment Study (FATS) cohort were subgrouped into those with triglyceride levels \leq 120 mg/dL (n = 26) and those with triglyceride levels \geq 190 mg/dL (n = 40). Their therapeutic responses to niacin plus colestipol, lovastatin plus colestipol, colestipol alone, or placebo were determined. Therapeutic response was also determined in the same 2 triglyceride subgroups (n = 12 and n = 27, respectively) of patients selected for low levels of high-density lipoprotein (HDL) cholesterol and coronary artery disease. These triglyceride criteria were chosen to identify patient subgroups with high likelihood of "pattern A" (normal-size low-density lipoprotein [LDL] particles and triglyceride \leq 120 mg/dL) or "pattern B" (small dense LDL and triglyceride \geq 190 mg/dL). Our findings in these small patient subgroups are consistent with the emerging understanding that coronary artery disease patients presenting with high triglyceride levels have lower HDL-C, smaller less buoyant LDL-C, and greater very low-density lipoprotein (VLDL) cholesterol and VLDL apolipoprotein B, and are more responsive to therapy as assessed by an increase in HDL-C and reduction in triglycerides, VLDL-C, and VLDL apolipoprotein B. In

the FATS high-triglyceride subgroup with these characteristics, a tendency toward greater therapeutic improvement in coronary stenosis severity was observed among those treated with either of the 2 forms of intensive cholesterol -lowering therapy. This improvement is associated with therapeutic reduction of LDL-C and elevation of HDL-C, but also appears to be associated with drug-induced improvement in LDL buoyancy. (20 Refs.)

Hypocoagulant and lipid-lowering effects of dietary n-3 polyunsaturated fatty acids with unchanged platelet activation in rats.

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Arterioscler Thromb Vasc Biol (United States) Sep 1998, 18 (9) p1480-9

We investigated the effects of dietary polyunsaturated fatty acids (PUFAs) on blood lipids and processes that determine hemostatic potential: platelet activation, coagulation, and fibrinolysis. For 8 to 10 weeks, Wistar rats were fed a high-fat diet containing various amounts (2% to 16%) of n-3 PUFAs derived from fish oil (FO) or a diet enriched in n-6 PUFAs from sunflower seed oil (SO). Only the FO diets caused a reduction in mean platelet volume, platelet arachidonate level, and formation of thromboxane B₂ by activated platelets, but neither of the diets had a measurable effect on platelet activation. The FO-rich diets decreased the plasma concentrations of triglycerides and cholesterol, whereas the SO diet reduced triglycerides only. Parameters of fibrinolysis and standard coagulation times, ie, activated partial thromboplastin time and prothrombin time, were only marginally influenced by these diets. In contrast, dietary FO, but not SO, led to decreased levels of the vitamin K-dependent coagulation factors prothrombin and factor VII, while the level of antithrombin III was unchanged. The endogenous thrombin potential (ETP) was measured with an assay developed to detect the hypocoagulable state of plasma. After activation with tissue factor and phospholipids, the ETP was reduced by 23% or more in plasma from animals fed a diet with >4% FO. No significant effect of the SO diet on ETP was observed. Control experiments with plasma from warfarin-treated rats indicated that the ETP was more sensitive to changes in prothrombin concentration than in factor VII concentration. Taken together, these results indicate that in rats, prolonged administration of n-3 but not n-6 PUFAs can lead to a hypocoagulable state of plasma through a reduced capacity of vitamin K-dependent thrombin generation, with unchanged thrombin inactivation by antithrombin III.

Effects of dietary fish oil on serum lipids and VLDL kinetics in hyperlipidemic apolipoprotein E*3-Leiden transgenic mice.

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J Lipid Res (United States) Jun 1998, 39 (6) p1181-8

Studying the effects of dietary fish oil on VLDL metabolism in humans is subject to both large intra- and interindividual variability. In the present study we therefore used hyperlipidemic apolipoprotein (APO) E*3-Leiden mice, which have impaired chylomicron and very low density lipoprotein (VLDL) remnant metabolism, to study the effects of dietary fish oil on serum lipids and VLDL kinetics under highly standardized conditions. For this, female APOE*3-Leiden mice were fed a fat- and cholesterol -containing diet supplemented with either 0, 3 or 6% w/w (i.e. 0, 6, or 12% of total energy) of fish oil. Fish oil -fed mice showed a significant dose-dependent decrease in serum cholesterol (up to -43%) and triglyceride levels (up to -60%), mainly due to a reduction of VLDL (-80%). LDL and HDL cholesterol levels were not affected by fish oil feeding. VLDL-apoB kinetic studies showed that fish oil feeding resulted in a significant 2-fold increase in VLDL-apoB fractional catabolic rate (FCR). Hepatic VLDL-apoB production was, however, not affected by fish oil feeding. VLDL-triglyceride turnover studies revealed that fish oil significantly decreased hepatic VLDL-triglyceride production rate (-60%). A significant increase in VLDL-triglyceride FCR was observed (+70%), which was not related to increased lipolytic activity. We conclude that APOE*3-Leiden mice are highly responsive to dietary fish oil. The observed strong reduction in serum very low density lipoprotein (VLDL) is primarily due to an effect of fish oil to decrease hepatic VLDL triglyceride production rate and to increase VLDL-apoB fractional catabolic rate.

Effect of fish - oil -enriched margarine on plasma lipids, low-density-lipoprotein particle composition, size, and susceptibility to oxidation.

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Am J Clin Nutr (United States) Aug 1998, 68 (2) p235-41

We investigated the effect of incorporating n-3 polyunsaturated fatty acids (PUFAs) into the diet on the lipid-class composition of LDLs, their size, and their susceptibility to oxidation. Forty-seven healthy volunteers incorporated 30 g sunflower-oil (SO) margarine/d into their habitual diet during a 3-wk run-in period and then used either SO or a fish -oil -enriched sunflower oil (FO) margarine for the following 4 wk. Plasma concentrations of total cholesterol, triacylglycerols, HDL cholesterol, LDL cholesterol, and apolipoproteins A-I and B did not differ significantly between the groups during intervention. The FO margarine increased the concentration of n-3 very-long-chain PUFAs in the LDL particles, showing 93% ($P < 0.0001$), 8% ($P = 0.05$), and 35% ($P < 0.0001$) increases in eicosapentaenoic acid, docosapentaenoic acid, and docosahexaenoic acid, respectively, in the FO group compared with 3%, 7%, and 7%, respectively,

in the SO group during the intervention. The cholesterol content of the LDL particles increased in the FO group [total cholesterol : 6% (P = 0.008); cholesterol ester: 12% (P = 0.014)], although it was not significantly different from that in the control group, whereas the other lipid classes and the size of the LDL particles remained unchanged in both groups. A reduction in the alpha-tocopherol content in LDL (6%, P = 0.005) was observed in the FO group. Ex vivo oxidation of LDL induced with Cu²⁺ showed a significantly reduced lag time (from 91 to 86 min, P = 0.003) and lower maximum rate of oxidation (from 10.5 to 10.2 nmol x mg⁻¹) x min⁻¹, P = 0.003) after intake of the FO margarine. The results indicate that consumption of the FO compared with the SO margarine had no effect on LDL size and lipid composition and led to minor changes in LDL a-tocopherol content and oxidation resistance.

Abnormal content of n-6 and n-3 long-chain unsaturated fatty acids in the phosphoglycerides and cholesterol esters of parahippocampal cortex from Alzheimer's disease patients and its relationship to acetyl CoA content.

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Int J Biochem Cell Biol (England) Feb 1998, 30 (2) p197-207

The long-chain fatty acid composition of cholesterol esters, phosphatidylcholine (PC), phosphatidylethanolamine (PE), phosphatidylserine (PS) and phosphatidylinositol (PI) from parahippocampal cortex of Alzheimer's disease (AD) patients and control subjects was examined. In general the PC fraction contained less polyunsaturated long-chain fatty acids than did PE, PS or PI. Of the n-6 polyunsaturated long-chain fatty acids, PI contained the greatest incorporation of these acids followed by PE. There were significant differences between controls and AD patients in total n-6 EFAs. Arachidonic acid (C_{20:4n-6}) was the predominant fatty acid of this family found to be present. In AD, PE and PS showed a deficit of adrenic acid (C_{22:4n-6}) content and PE also contained less arachidonic acid. In AD subjects, the cholesterol esters contained significantly less n-3 polyunsaturated fatty acids with, specifically, a reduction in alpha-linolenic acid. Acetyl CoA content of hippocampal cortex was greater in AD patients than in control subjects indicating either an increased extent of oxidative metabolism or a failure to utilise acetyl CoA for anabolic processes. Abnormal magnitude of oxidative processes could give rise to the biosynthesis of PE and PS species containing less n-6 polyunsaturated fatty acids than occurs in control subjects.

Mediterranean dietary pattern in a randomized trial: prolonged survival and possible reduced cancer rate

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BACKGROUND: The Mediterranean dietary pattern is thought to reduce the risk of cancer in addition to being cardioprotective. However, no trial has been conducted so far to prove this belief.

METHODS: We compared overall survival and newly diagnosed cancer rate among 605 patients with coronary heart disease randomized in the Lyon Diet Heart Study and following either a cardioprotective Mediterranean-type diet or a control diet close to the step 1 American Heart Association prudent diet.

RESULTS: During a follow-up of 4 years, there were a total of 38 deaths (24 in controls vs 14 in the experimental group), including 25 cardiac deaths (19 vs 6) and 7 cancer deaths (4 vs 3), and 24 cancers (17 vs 7). Exclusion of early cancer diagnoses (within the first 24 months after entry into the trial) left a total of 14 cancers (12 vs 2). After adjustment for age, sex, smoking, leukocyte count, cholesterol level, and aspirin use, the reduction of risk in experimental subjects compared with control subjects was 56% ($P=.03$) for total deaths, 61% ($P=.05$) for cancers, and 56% ($P=.01$) for the combination of deaths and cancers. The intakes of fruits, vegetables, and cereals were significantly higher in experimental subjects, providing larger amounts of fiber and vitamin C ($P<.05$). The intakes of cholesterol and saturated and polyunsaturated fats were lower and those of oleic acid and omega - 3 fatty acids were higher ($P<.001$) in experimental subjects. Plasma levels of vitamins C and E ($P<.05$) and omega -3 fatty acids ($P<.001$), measured 2 months after randomization, were higher and those of omega-6 fatty acids were lower ($P<.001$) in experimental subjects.

CONCLUSIONS: This randomized trial suggests that patients following a cardioprotective Mediterranean diet have a prolonged survival and may also be protected against cancer. Further studies are warranted to confirm the data and to explore the role of the different lipids and fatty acids in this protection.

Dietary (n-3) and (n-6) polyunsaturated fatty acids rapidly modify fatty acid composition and insulin effects in rat adipocytes.

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J Nutr (United States) Mar 1998, 128 (3) p512-9

The influence of dietary (n-3) compared with (n-6) polyunsaturated fatty acids (PUFA) on the lipid composition and metabolism of adipocytes was evaluated in rats over a period of 1 week. Isocaloric diets comprised 16.3 g/100 g protein, 53.8 g/100 g carbohydrate and 21.4 g/100 g lipids, the latter containing either (n-3) PUFA (32.4 mol/100 mol) or (n-6) PUFA (37.8 mol/100 mol) but having identical contents of saturated, monounsaturated and total unsaturated fatty acids and

identical polyunsaturated to saturated fatty acid ratios and double bond indexes. Despite comparable food intake, significantly smaller body weight increments and adipocyte size were observed in rats of the (n-3) diet group after feeding for 1 wk. Rats fed the (n-3) diet also had significantly lower concentrations of serum triglycerides, cholesterol and insulin compared with those fed the (n-6) diet, although levels of serum glucose and free fatty acids did not differ in the two dietary groups. In the (n-6) diet group, the (n-6) and (n-3) PUFA contents of plasma triglycerides, free fatty acids and phospholipids were 30-60% higher and 60-80% lower, respectively, than in the (n-3) diet group, whereas adipocyte plasma membrane phospholipids showed a significantly higher unsaturated to saturated fatty acid ratio and greater fluidity. Glycerol release in response to noradrenaline was significantly higher in the adipocytes of rats fed the (n-3) diet, whereas the antilipolytic effect of insulin generally did not differ in the two groups. Finally, insulin stimulated the transport of glucose and its incorporation into fatty acids to a lesser extent in adipocytes of (n-3) diet fed rats compared with (n-6) diet fed rats. This reduction in the metabolic effects of insulin in rats fed a (n-3) diet for 1 wk could be related to smaller numbers and a lower binding capacity of the insulin receptors on adipocytes and/or to a lesser degree of phosphorylation of the 95 kDa beta subunit of the receptor. In conclusion, dietary intake for 1 wk of (n-3) rather than (n-6) PUFA is sufficient to induce significant differences in the lipid composition and metabolic responses to insulin of rat adipocytes.

Effects of omega- 3 fatty acids and/or antioxidants on endothelial cell markers

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European Journal of Clinical Investigation (United Kingdom), 1998, 28/8 (629-635)

Background. Increased expression of cell adhesion molecules and increased procoagulant activity of the vascular endothelium have been postulated to characterize dysfunctional endothelium. The cellular effects of n-3 fatty acids (n-3 FAs) and antioxidants are still not clarified.

Methods. In a randomized, factorial two-by-two design study, we have investigated 41 male smokers with hyperlipidaemia before and after 6 weeks of supplementation with either n-3 FAs (4.8 g daily) or placebo with the addition of antioxidants (1.50 mg of vitamin C, 75 mg of vitamin E and 15 mg of p-carotene daily) or placebo with regard to the effects on some endothelial cell markers: thrombomodulin (sTM), von Willebrand factor (vWF), tissue plasminogen activator antigen (tPAag) and soluble forms of the cell adhesion molecules E-selectin, P-selectin and vascular cell adhesion molecule 1 (VCAM-1).

Results. In the n-3 FA group, significant reductions in the plasma levels of vWF (P = 0.034) and sTM (P<0.001) were demonstrated compared with placebo, whereas increased levels were found for E-selectin (P = 0.001) and VCAM-1 (P = 0.010). In the antioxidant group, no differences in changes were noted for any of the variables.

Conclusion. The reduction in the levels of sTM and VWF with n-3 FA supplementation could indicate an improvement with regard to the haemostatic markers of endothelial dysfunction, whereas the simultaneous increase in the soluble forms of E-selectin and VCAM-1 may suggest an adverse effect on the inflammatory system. The antioxidants seem to be neutral in their effect on these endothelial cell markers in our study population of smokers. The interpretation of the soluble forms of these molecules are, however, still debatable.

Omega-3 ethyl ester concentrate decreases total apolipoprotein CIII and increases antithrombin III in postmyocardial infarction patients

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Clinical Drug Investigation (New Zealand), 1998, 15/6 (473-482)

This study investigated whether an ethyl ester preparation of fish oil (omega-3) could normalise raised plasma concentrations of triglycerides, apolipoprotein CIII on apolipoprotein B-containing particles (LP CIII:B) found in patients with recent acute myocardial infarction. We also studied the effect of fish oil on antithrombin III levels. Out of 75 patients with a plasma triglyceride value less than or equal to 2.0 mmol/L, 22 normalised their triglycerides during diet and were therefore not randomised. The remaining patients were randomly assigned to 12 weeks' treatment with a daily dose of 4g omega-3 or placebo. Mean plasma triglyceride concentrations were reduced by 24% from 3.10 plus or minus 1.15 (SD) to 2.53 plus or minus 0.94 mmol/L (p < 0.001) on omega-3 (p < 0.001 vs placebo). The reduction was due to decreases in very low density lipoprotein concentrations. Total apolipoprotein CIII decreased significantly. This was due to reductions in LP CIII:non B concentrations, but the ratio LP CIII:non B/LP CIII:B was unaffected because of a slight insignificant decrease in LP CIII:B. The plasma triglyceride decreasing effect of omega-3 could therefore not be due to redistribution of CIII between lipoproteins. Low density lipoprotein (LDL) cholesterol increased significantly with omega-3 by 7%, and antithrombin III increased significantly with fish oil. In conclusion, omega-3 had a moderate plasma triglyceride lowering effect and increased LDL cholesterol slightly, while antithrombin III increased in patients with hypertriglyceridaemia who had recently experienced a myocardial infarction. Myocardial infarction starts via a thrombotic process at an atherosclerotic lesion in a coronary artery. Most patients developing this disease have an abnormal plasma lipoprotein pattern consisting of slightly raised triglycerides (TGs), moderately elevated total cholesterol, and low high density lipoprotein (HDL) cholesterol values predisposing to atherosclerosis.

Hypertriglyceridaemia may be associated with a greater risk for thrombosis in postmyocardial infarction patients because of a reduced fibrinolytic capacity. The dyslipidaemia may also indicate an unfavourable distribution of plasma lipoprotein particles in patients with myocardial infarction. Dietary changes normalise the dyslipidaemia in some patients but are inadequate in others. In these latter patients pharmacological lipid-lowering treatment is necessary. The myocardial infarction patient with an athero-thrombogenic syndrome could theoretically therefore benefit from a pharmacological agent acting on both the thrombotic and lipidaemic pathophysiological pathways. The pharmacological potency of the omega -3 -fatty acids allows for this possibility. It has been known since the mid 1970s that omega -3 -fatty acids are effective in lowering plasma triglyceride concentrations. They also increase the concentration of HDL cholesterol slightly. Their effects on cholesterol have varied, with some studies showing increases and others decreases. These fatty acids also inhibit platelet aggregation. It was therefore of interest to expand the experience of this type of treatment to effects on plasma lipoprotein particle distribution. We also studied parameters of fibrinolysis since the literature shows diverging results of omega - 3 - fatty acids on these parameters. In the present study we tested a new compound, omega-3, an oil consisting of ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), with the aim of normalising dyslipidaemia, and reducing the thrombotic tendency in a potentially important target population for such treatment, postmyocardial infarction patients. The high EPA and DHA concentration in omega-3 made a convenient intake of only four capsules daily possible. The design of the study followed the current guidelines for secondary prevention of ischaemic heart disease.

One-year treatment with ethyl esters of n-3 fatty acids in patients with hypertriglyceridemia and glucose intolerance reduced triglyceridemia, total cholesterol and increased HDL-C without glycemic alterations

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Atherosclerosis (Ireland), 1998, 137/2 (419-427)

n-3 Fatty acids in the form of ethyl esters (EE) allow lower daily doses and improved compliance. Administration of n-3 fatty acids to patients with glucose intolerance has led to controversial findings, some studies indicating worsening of the disorder, others no effect, or an improvement. A total of 935 patients with hypertriglyceridemia, associated with additional cardiovascular risk factors, i.e. glucose intolerance, NIDDM and/or arterial hypertension were entered a double blind (DB) protocol lasting 6 months with n-3 BE versus placebo, followed by a further 6 months of open study (n = 868) on 2 g a day of n-3 EE. At the end of the DB period, triglyceridemia in the total group was reduced significantly more by n-3 EE, without alterations in glycemic parameters. In the 6 months open follow up, patients on n-3 EE with type IIB hyperlipoproteinemia showed a significant reduction of total cholesterol, both in cases with (- 4.15% vs. the 6 month levels)

and without NIDDM (- 3.8%). HDL-cholesterol had an overall mean rise of 7.4%, maximal in type IV patients with (+9.1%) and without (+ 10.1%) NIDDM. No alterations in glycemic parameters were detected in treated patients. Administration of n-3 EE to patients with hypertriglyceridemia associated with NIDDM or impaired glucose tolerance appears safe and effective.

The effects of an omega-3 ethyl ester concentrate on blood lipid concentrations in patients with hyperlipidaemia

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Clinical Drug Investigation (New Zealand), 1998, 15/5 (397-404)

The objective of this study was to investigate the effects and tolerability of an omega-3 ethyl ester concentrate (Omacor (R)) on serum lipid concentrations in patients with hyperlipidaemia. A multicentre, double-blind, randomised, placebo-controlled trial was performed in the hospital and general practice setting. 84 patients with hyperlipidaemia were given a therapeutic lipid-lowering diet for 10 weeks. Of these, 55 patients were randomised to a 12-week treatment period. 47 patients completed the study and two patients withdrew because of adverse events. Randomised patients received omega-3 ethyl ester concentrate or corn oil (placebo), both administered at a dose of 2 g twice daily in soft gelatin capsules. Main outcome measures included changes in eicosapentaenoic acid (EPA)/docosahexaenoic acid (DHA) content of serum phospholipids, total serum triglycerides, total serum cholesterol, and high density lipoprotein (HDL) cholesterol between baseline (week 10) and the end of treatment (week 22). After 12 weeks of treatment, patients receiving the omega-3 ethyl ester concentrate showed a significant increase in the EPA/DHA content of serum phospholipids ($p < 0.0001$). No significant changes in serum phospholipids were observed in the patients given placebo. A mean [standard deviation (SD)] reduction in serum triglyceride of 28.3 (19.1)% ($p = 0.0001$) occurred in patients given the omega-3 ethyl ester concentrate. Patients receiving corn oil showed a nonsignificant mean (SD) increase in serum triglyceride of 9.1 (24.8)%. Therefore, a difference between the groups of 37.4% in favour of active treatment was found ($p < 0.0001$). Total serum cholesterol did not change significantly in either treatment group. Mean (SD) HDL cholesterol concentrations showed an increase of 0.9 (21.6)% in patients receiving omega-3 ethyl ester concentrate and 3.6 (24.3)% in the corn-oil group; however, neither increase was significant. In conclusion, omega-3 ethyl ester concentrate, 4 g/day, produced a significant reduction in mean serum triglyceride concentration in patients with hyperlipidaemia and was well tolerated.

On the effect of 2-deuterium- and 2-methyl-eicosapentaenoic acid derivatives on triglycerides, peroxisomal beta-oxidation and platelet aggregation in rats

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(193-203)

A series of 2-substituted eicosapentaenoic acid (EPA) derivatives (as ethyl esters) have been synthesized and evaluated as hypolipidemic and antithrombotic agents in feeding experiments in rats. Repeated administration of purified 2-methyleicosapentaenoic acid and its deuterium analogues (all as ethyl esters) to rats resulted in a decrease in plasma triglycerides and high density lipoprotein cholesterol. The 2-methyl-EPA analogues were, apparently, four times more potent than EPA in inducing the triglyceride lowering effect. The 2-deuterium-2-methyl-EPA decreased plasma cholesterol level to similar 40%. A moderate enlargement of the liver was observed in 2-methyl-EPA treated rats. This was accompanied with an acute reduction in the liver content of triglycerides and a stimulation of peroxisomal beta-oxidation and fatty acyl-CoA oxidase activity. The results suggest that the triglyceride-lowering, effect of 2-methyl-EPA may be due to a reduced supply of fatty acids for hepatic triglyceride biosynthesis because of increased fatty acid oxidation. Platelet aggregation with ADP and A23187 was performed *ex vivo* in platelet-rich plasma, after administration of different doses of the EPA-derivatives for five days. EPA and 2,2-dideuterium EPA had no effect on ADP-induced aggregation, while 2-deuterium-, 2-methyl- and 2-deuterium-2-methyl EPA produced a biphasic effect, i.e. potentiation and inhibition at low (250 mg/day kg body weight) and higher doses (600-1300 mg/day kg body weight), respectively. A23187-induced platelet aggregation was affected in a similar way by feeding the 2-substituted EPA derivatives, except that 2-deuterium-2-methyl EPA had no effect relative to EPA itself and that the inhibition was far greater than that for ADP-induced aggregation (similar 100% inhibition with 600 mg 2-methyl-EPA/day kg body weight). The ranking order of the EPA-derivatives to affect platelet aggregation and to cause hypolipidemia was different, suggesting different mechanisms. Our observations suggest that the effects of the EPA derivatives on platelet aggregation could be related to the degree of bulkiness around C2 and that an asymmetric substitution at C2 caused inhibition of platelet aggregation while a symmetric substitution did not. It is suggested that the bulky, asymmetric derivatives inhibit platelet aggregation by altering platelet membrane phospholipid packing.

Effect of garlic (*Allium sativum*) on blood lipids, blood sugar, fibrinogen and fibrinolytic activity in patients with coronary artery disease.

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Prostaglandins Leukot Essent Fatty Acids (Scotland) Apr 1998, 58 (4) p257-63

Thirty patients with coronary artery disease (CAD) were administered garlic (study group) while another 30 patients received the placebo (control group).

Various risk parameters were determined at 1.5 and 3 months of garlic administration. Garlic, administered in a daily dose of 2 x 2 capsules (each capsule containing ethyl acetate extract from 1 g peeled and crushed raw garlic), reduced significantly total serum cholesterol and triglycerides, and increased significantly HDL-cholesterol and fibrinolytic activity. There was no effect on the fibrinogen and glucose levels. In vitro effects of the garlic oil on platelet aggregation (PAG) and eicosanoid metabolism were examined; it inhibited PAG induced by several platelet agonists, and also platelet thromboxane formation. Two important paraffinic polysulphides - diallyl disulphide (DADS) and diallyl trisulphide (DATS) - derived from garlic and are usual constituents of garlic oil, showed antiplatelet activity, and also inhibited platelet thromboxane formation. In this respect DATS was more potent than DADS. The nature of inhibition of PAG by DATS was found to be reversible.

Garlic powder and plasma lipids and lipoproteins: a multicenter, randomized, placebo-controlled trial.

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BACKGROUND: Garlic powder tablets have been reported to lower serum cholesterol levels. There is widespread belief among the general public that garlic powder tablets aid in controlling cholesterol levels. However, much of the prior data demonstrating the cholesterol-lowering effect of garlic tablets involved studies that were inadequately controlled.

OBJECTIVE: To determine the lipid-lowering effect of garlic powder tablets in patients with hypercholesterolemia.

METHODS: This was a randomized, double-blind, placebo-controlled, 12-week, parallel treatment study carried out in 2 outpatient lipid clinics. Entry into the study after 8 weeks of diet stabilization required a mean low-density lipoprotein cholesterol level on 2 visits of 4.1 mmol/L (160 mg/dL) or lower and a triglyceride level of 4.0 mmol/L (350 mg/dL) or lower. The active treatment arm received tablets containing 300 mg of garlic powder (Kwai) 3 times per day, given with meals (total, 900 mg/d). This is equivalent to approximately 2.7 g or approximately 1 clove of fresh garlic per day. The placebo arm received an identical-looking tablet, also given 3 times per day with meals. The main outcome measures included levels of total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol after 12 weeks of treatment.

RESULTS: Twenty-eight patients (43% male; mean +/- SD age, 58 +/- 14 years) received garlic powder treatment and 22 (68% male; mean +/- SD age, 57 +/- 13 years) received placebo treatment. There were no significant lipid or lipoprotein

changes in either the placebo- or garlic -treated groups and no significant difference between changes in the placebo-treated group compared with changes in the garlic -treated patients.

CONCLUSION: Garlic powder (900 mg/d) treatment for 12 weeks was ineffective in lowering cholesterol levels in patients with hypercholesterolemia.

Effect of a garlic oil preparation on serum lipoproteins and cholesterol metabolism: a randomized controlled trial.

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JAMA (United States) Jun 17 1998, 279 (23) p1900-2

CONTEXT: Garlic -containing drugs have been used in the treatment of hypercholesterolemia even though their efficacy is not generally established. Little is known about the mechanisms of action of the possible effects on cholesterol in humans.

OBJECTIVE: To estimate the hypocholesterolemic effect of garlic oil and to investigate the possible mechanism of action.

DESIGN: Double-blind, randomized, placebo-controlled trial.

SETTING: Outpatient lipid clinic.

PATIENTS: We investigated 25 patients (mean age, 58 years) with moderate hypercholesterolemia.

INTERVENTION: Steam-distilled garlic oil preparation (5 mg twice a day) vs placebo each for 12 weeks with wash-out periods of 4 weeks.

MAIN OUTCOME MEASURES: Serum lipoprotein concentrations, cholesterol absorption, and cholesterol synthesis.

RESULTS: Baseline lipoprotein profiles were (mean [SD]): total cholesterol , 7.53 (0.75) mmol/L (291 [29] mg/dL); low-density lipoprotein cholesterol (LDL-C), 5.35 (0.78) mmol/L (207 [30] mg/dL); high-density lipoprotein cholesterol (HDL-C), 1.50 (0.41) mmol/L (58 [16] mg/dL); and triglycerides, 1.45 (0.73) mmol/L (127 [64] mg/ dL). Lipoprotein levels were virtually unchanged at the end of both treatment periods (mean difference [95% confidence interval]): total cholesterol , 0.085 (-0.201 to 0.372) mmol/L (3.3 [-7.8 to 14.4] mg/dL), P=.54; LDL-C, 0.001 (-0.242 to 0.245) mmol/L (0.04 [-9.4 to 9.5] mg/dL), P=.99; HDL-C, 0.050 (-0.028 to 0.128) mmol/L (1.9 [-1.1 to 4.9] mg/dL), P=.20; triglycerides, 0.047 (-0.229 to 0.135) mmol/L (4.2 [-20.3 to 12.0]) mg/dL, P=.60. Cholesterol absorption (37.5% [10.5%] vs 38.3% [10.7%]), P=.58, cholesterol synthesis

(12.7 [6.5] vs 13.4 [6.6] mg/kg of body weight per day, $P=.64$), mevalonic acid excretion (192 [66] vs 187 [66] microg/d, $P=.78$), and changes in the ratio of lathosterol to cholesterol in serum (4.4% [24.3%] vs 10.6% [21.1%], $P=.62$) were not different in garlic and placebo treatment.

CONCLUSIONS: The commercial garlic oil preparation investigated had no influence on serum lipoproteins, cholesterol absorption, or cholesterol synthesis. Garlic therapy for treatment of hypercholesterolemia cannot be recommended on the basis of this study.

[Influence of lifestyle on the use of supplements in the Brandenburg nutrition and cancer study]

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Z Ernährungswiss (Germany) Mar 1998, 37 (1) p38-46

Differences in dietary habits and lifestyle factors associated with a high dietary intake of fruit and vegetables are discussed and used to explain the disparity between results of observational epidemiologic studies consistently showing antioxidative vitamins to exert a protective effect on chronic diseases, and intervention studies so far not confirming this association. Within the scope of the "Brandenburger Ernährungs- und Krebsstudie", the East German contribution to the European Prospective Investigation into Cancer and Nutrition (EPIC), we examined whether study participants using supplements on a regular basis--minerals, vitamins, protein formulation, bran/linseed, fiber, yeast or garlic pills--differed from those who did not report use of supplements according to selected lifestyle factors and dietary intake of vitamins, minerals, fiber, cholesterol, and fat from food. The study sample consisted of 10,522 participants (4,500 men and 6,022 women) aged 35-65 years enrolled in the cohort from January 1995 to July 1996. Regular intake of one or more supplements during the past year was reported by 32.6% of women and 25.5% of men. Vitamin supplements were used by 18.8% of the women and 15.8% of the men. Figures for minerals were 14.2% for women and 8.6% for men, respectively. Garlic pills were taken regularly by 9.7% of men and 9.3% of women. Prevalence of supplement use was generally higher in women and was more pronounced in elderly participants. The most frequently used combinations were vitamin and mineral supplements, followed by a combination of garlic and either vitamin or mineral supplements. Increased use of supplements was significantly associated with higher level of education attained, regular engagement in sporting activities, health complaints, and dietary change during the previous year. No association between use of supplements and smoking status nor elevated alcohol consumption was observed. Body mass index above 30 was significantly related to increased intake of garlic pills, and in women to significantly increased use of vitamin and mineral supplements. For both men and women, age-adjusted consumption of fruit and vegetables and intake of vitamins, minerals, and fiber from food was higher for participants using mineral but also vitamin supplements compared to those who did not use these

supplements. For the cohort of the "Brandenburger Ernährungs- und Krebsstudie" we observed on the one hand that age, gender, and health-conscious lifestyle factors were related to supplement use. On the other hand presence of subjective health complaints was related to supplement use, especially for use of vitamins and minerals. Participants, who regularly consumed minerals and vitamins were also shown to have a higher intake of foods and nutrients considered to exert an antioxidative effect.

In vitro effect of garlic powder extract on lipid content in normal and atherosclerotic human aortic cells.

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Lipids (United States) Oct 1997, 32 (10) p1055-60

In the present study, the mechanism of the in vitro effect of garlic powder extract (GPE) on lipid content of cultured human aortic cells was investigated. The addition of GPE abolished atherogenic blood serum-induced accumulation of free cholesterol, triglycerides, and cholesteryl esters in smooth muscle cells derived from uninvolved (normal) intima. In cells isolated from atherosclerotic plaque, GPE lowered these lipids. GPE inhibited lipid synthesis both in normal and atherosclerotic cells. It inhibited acyl-CoA:cholesterol acyltransferase activity that participates in the cholesteryl ester formation and stimulated cholesteryl ester hydrolase that degrades cholesteryl esters. This may explain the lipid reduction caused by GPE in atherosclerotic cells. GPE inhibited the uptake of modified low density lipoprotein and degradation of lipoprotein-derived cholesteryl esters, thus considerably reducing the intracellular accumulation of cholesteryl esters. This suggests the mechanism responsible for the prevention of lipid accumulation in aortic cells caused by atherogenic blood serum.

Modulation of lipid profile by fish oil and garlic combination.

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J Natl Med Assoc (United States) Oct 1997, 89 (10) p673-8

Fish consumption has been shown to influence epidemiology of heart disease, and garlic has been shown to influence triglyceride levels. This study was undertaken to evaluate the effect of fish oil and garlic combinations as a dietary supplement on the lipid subfractions. Forty consecutive subjects with lipid profile abnormalities were enrolled in a single-blind, placebo-controlled crossover study. Each subject received placebo for 1 month and fish oil (1800 mg of eicosapentanoic acid [EPA] + 1200 mg of docosahexanoic acid) with garlic powder (1200 mg) capsules daily for 1 month. Lipid fractionation was performed

prior to study initiation, after the placebo period, and after the intervention period. Subjects all had cholesterol levels > 200. Subjects were instructed to maintain their usual diets. Supplementation for 1 month resulted in an 11% decrease in cholesterol, a 34% decrease in triglyceride, and a 10% decrease in low-density lipoprotein (LDL) levels, as well as a 19% decrease in cholesterol /high-density lipoprotein (HDL) risk. Although not significant, there was a trend toward increase in HDL. There was no significant placebo effect. These results suggest that in addition to the known anticoagulant and antioxidant properties of both fish oil and garlic, the combination causes favorable shifts in the lipid subfractions within 1 month. Triglycerides are affected to the largest extent. The cholesterol lowering and improvement in lipid/HDL risk ratios suggests that these combinations may have antiatherosclerotic properties and may protect against the development of coronary artery disease.

Effect of garlic and fish-oil supplementation on serum lipid and lipoprotein concentrations in hypercholesterolemic men

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Am J Clin Nutr (United States) Feb 1997, 65 (2) p445-50

This study examined the effects of garlic and fish-oil supplementation (alone and in combination) on fasting serum lipids and lipoproteins in hypercholesterolemic subjects. After an initial run-in phase, 50 male subjects with moderate hypercholesterolemia were randomly assigned for 12 wk to one of four groups: 1) 900 mg garlic placebo/d + 12 g oil placebo/d; 2) 900 mg garlic /d + 12 g oil placebo/d; 3) 900 mg garlic placebo/d + 12 g fish oil/d, providing 3.6 g n-3 fatty acids/d; and 4) 900 mg garlic /d + 12 g fish oil/d. In the placebo group, mean serum total cholesterol, low-density-lipoprotein cholesterol (LDL-C), and triacylglycerols were not significantly changed in relation to baseline. Mean group total cholesterol concentrations were significantly lower with garlic +fish oil (-12.2%) and with garlic (-11.5%) after 12 wk but not with fish oil alone. Mean LDL-C concentrations were reduced with garlic +fish oil (-9.5%) and with garlic (-14.2%) but were raised with fish oil (+8.5%). Mean triacylglycerol concentrations were reduced with garlic +fish oil (-34.3%) and fish oil alone (-37.3%). The garlic groups (with and without fish oil) had significantly lower ratios of total cholesterol to high-density-lipoprotein cholesterol (HDL-C) and LDL-C to HDL-C. In summary, garlic supplementation significantly decreased both total cholesterol and LDL-C whereas fish-oil supplementation significantly decreased triacylglycerol concentrations and increased LDL-C concentrations in hypercholesterolemic men. The combination of garlic and fish oil reversed the moderate fish-oil-induced rise in LDL-C. Coadministration of garlic with fish oil was well-tolerated and had a beneficial effect on serum lipid and lipoprotein concentrations by providing a combined lowering of total cholesterol, LDL-C, and triacylglycerol concentrations as well as the ratios of total cholesterol to HDL-C and LDL-C to HDL-C.

Garlic powder in the treatment of moderate hyperlipidaemia: a controlled trial and meta-analysis.

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J R Coll Physicians Lond (England) Jul-Aug 1996, 30 (4) p329-34

OBJECTIVE: To determine the effect of 900 mg/day of dried garlic powder (standardised to 1.3% allicin) in reducing total cholesterol .

DESIGN: Double-blind, randomised six-month parallel trial.

SUBJECTS: 115 individuals with a repeat total cholesterol concentration of 6.0-8.5 mmol/l and low-density lipoprotein (LDL) cholesterol of 3.5 mmol/l or above after six weeks of dietary advice.

INTERVENTION: The active treatment group received dried garlic tablets (standardised to 1.3% allicin) at a dosage of 300 mg three times daily. The control group received a matching placebo.

OUTCOME MEASURES: Primary end-point: total cholesterol concentration; secondary end-points: concentrations of LDL and high-density lipoprotein cholesterol , apolipoproteins (apo) A1 and B, and triglycerides.

RESULTS: There were no significant differences between the groups receiving garlic and placebo in the mean concentrations of serum lipids, lipoproteins or apo A1 or B, by analysis either on intention-to-treat or treatment received. In a meta-analysis which included the results from this trial, garlic was associated with a mean reduction in total cholesterol of -0.65 mmol/l (95% confidence intervals: -0.53 to -0.76).

CONCLUSIONS: In this trial, garlic was less effective in reducing total cholesterol than suggested by previous meta-analyses. Possible explanations are publication bias, overestimation of treatment effects in trials with inadequate concealment of treatment allocation, or a type 2 error. We conclude that meta-analyses should be interpreted critically and with particular caution if the constituent trials are small.

Isolation of cholesteryl ester transfer protein inhibitors from Panax ginseng roots.

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Chem Pharm Bull (Tokyo) (Japan) Feb 1996, 44 (2) p444-5

We have isolated cholesteryl ester transfer protein (CETP) inhibitors from the extract of Korean Panax ginseng C. A. Meyer roots and identified them as polyacetylene analogs. These compounds inhibit human CETP with IC50 values of around 20-35 mg/ml.

A double-blind crossover study in moderately hypercholesterolemic men that compared the effect of aged garlic extract and placebo administration on blood lipids.

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Am J Clin Nutr (United States) Dec 1996, 64 (6) p866-70

A double-blind crossover study comparing the effect of aged garlic extract with a placebo on blood lipids was performed in a group of 41 moderately hypercholesterolemic men [cholesterol concentrations 5.7-7.5 mmol/L (220-290 mg/dL)]. After a 4-wk baseline period, during which the subjects were advised to adhere to a National Cholesterol Education Program Step I diet, they were started on 7.2 g aged garlic extract per day or an equivalent amount of placebo as a dietary supplement for a period of 6 mo, then switched to the other supplement for an additional 4 mo. Blood lipids, blood counts, thyroid and liver function measures, body weight, and blood pressure were followed over the entire study period. The major findings were a maximal reduction in total serum cholesterol of 6.1% or 7.0% in comparison with the average concentration during the placebo administration or baseline evaluation period, respectively. Low-density-lipoprotein cholesterol was also decreased by aged garlic extract, 4% when compared with average baseline values and 4.6% in comparison with placebo period concentrations. In addition, there was a 5.5% decrease in systolic blood pressure and a modest reduction of diastolic blood pressure in response to aged garlic extract. We conclude that dietary supplementation with aged garlic extract has beneficial effects on the lipid profile and blood pressure of moderately hypercholesterolemic subjects.

Perspectives on soy protein as a nonpharmacological approach for lowering cholesterol.

Goldberg AC
Department of Medicine, Washington University School of Medicine, St. Louis, MO 63110.
J Nutr (United States) Mar 1995, 125 (3 Suppl) p675S-678S

Dietary therapy is the first step in the treatment of hyperlipidemia. However, some patients are unable to lower their cholesterol concentrations to a desirable range with diet alone. For primary prevention of coronary artery disease,

physicians and patients often wish to avoid pharmacologic therapy of elevated cholesterol concentrations. The use of adjuncts to diet such as soluble fibers, garlic and soy protein may allow target lipid concentrations to be reached without the use of drugs. Soy protein incorporated into a low-fat diet can reduce cholesterol and LDL- cholesterol concentrations. The main obstacles to greater use of soy protein in the therapy of hyperlipidemia include lack of knowledge by physicians and patients of its effects and lack of availability of easily used products. Although soy products such as tofu and soymilk are available in many stores, consumers may be unaware of their presence and uses. Without the publication of articles in mainstream medical journals on the cholesterol - lowering effects of soy protein, few physicians are likely to know of possible uses. Readily available packaged products, recipes and cookbooks also will be necessary to make incorporation of soy protein into the American diet a reality. (30 Refs.)

Consumption of a garlic clove a day could be beneficial in preventing thrombosis.

Ali M; Thomson M

Department of Biochemistry, Faculty of Science, Kuwait University, Safat, Kuwait.

Prostaglandins Leukot Essent Fatty Acids (Scotland) Sep 1995, 53 (3) p211-2

The effect of the consumption of a fresh clove of garlic on platelet thromboxane production was examined. A group of male volunteers in the age range 40-50 years participated in the study. Each volunteer consumed one clove (approximately 3 g) of fresh garlic daily for a period of 16 weeks. Each participant served as his own control. Thromboxane B2 (TXB2, a stable metabolite of thromboxane A2), cholesterol and glucose were determined in serum obtained after blood clotting. After 26 weeks of garlic consumption, there was an approximately 20% reduction of serum cholesterol and about 80% reduction in serum thromboxane. No change in the level of serum glucose was observed. Thus, it appears that small amounts of fresh garlic consumed over a long period of time may be beneficial in the prevention of thrombosis.

On the effect of garlic on plasma lipids and lipoproteins in mild hypercholesterolaemia.

Simons LA; Balasubramaniam S; von Konigsmark M; Parfitt A; Simons J; Peters W

University of New South Wales Lipid Research Department, St Vincent's Hospital, Darlinghurst, Australia.

Atherosclerosis (Ireland) Mar 1995, 113 (2) p219-25

The ingestion of garlic has been reported to have many cardiovascular effects, including a reduction in plasma cholesterol concentration and the susceptibility of LDL to oxidation. A double-blind, placebo-controlled, randomised crossover study was conducted in subjects with mild to moderate hypercholesterolaemia who were subject to strict dietary supervision and assessment. After a baseline dietary period of 28 days, subjects took Kwai garlic powder tablets 300 mg three times daily or matching placebo for 12 weeks, followed by 28 days washout, followed by a 12 weeks crossover on the alternative preparation. In the analysis hypercholesterolaemia was defined as those subjects in the range 5.5-8.05 mmol/l. Three subjects were withdrawn, one allocated to garlic and complaining of garlic body odour, one using placebo having intercurrent health problems, and one with a baseline cholesterol below 5.5 mmol/l, yielding analysable results in 28 subjects. Comparing the period on garlic with that on placebo, there were no significant differences in plasma cholesterol, LDL cholesterol, HDL cholesterol, plasma triglycerides, lipoprotein(a) concentrations, or blood pressure. Mean LDL cholesterol concentration was 4.64 +/- 0.52 mmol/l on garlic and 4.60 +/- 0.59 mmol/l on placebo. There was no demonstrable effect of garlic on oxidisability of LDL, on the ratio of plasma lathosterol/ cholesterol (a measure of cholesterol synthesis), nor on LDL receptor expression in lymphocytes. This study found no demonstrable effect of garlic ingestion on lipids and lipoproteins.

Direct anti-atherosclerosis-related effects of garlic.

Orekhov AN; Tertov VV; Sobenin IA; Pivovarova EM
Institute of Experimental Cardiology, Russian Academy of Medical Sciences,
Moscow.
Ann Med (England) Feb 1995, 27 (1) p63-5

Direct anti-atherosclerosis-related effects of garlic were studied using cell culture. An aqueous extract from garlic powder (GPE) was added to smooth muscle cells cultured from atherosclerotic plaques of human aorta. During a 24-hour incubation, GPE significantly reduced the level of cholesteryl esters and free cholesterol in these cultured cells and inhibited their proliferative activity. In addition, GPE significantly reduced cholesterol accumulation and inhibited cell proliferation stimulated by blood serum taken from patients with angiographically assessed coronary atherosclerosis, i.e. GPE reduced atherogenic manifestations of patients' serum. Garlic effect on blood atherogenicity of patients with coronary atherosclerosis has also been studied ex vivo. Following a 24-hour incubation with cultured cells, patients' blood serum caused an increase of total cell cholesterol. Blood serum taken 2 hours after an oral administration of 300 mg garlic powder tablet caused substantially less cholesterol accumulation in cultured cells. This suggests that garlic powder manifests direct anti-atherogenic-related action not only in vitro but also in vivo.

Cardiovascular disease.

Gore JM; Dalen JE
University of Massachusetts Medical School, Worcester.
JAMA (United States) Jun 1 1994, 271 (21) p1660-1

The GUSTO angiographic trial helps to confirm the open artery theory.
Cholesterol levels in US adults continue to decrease. The consumption of one-half to one clove of garlic per day reduces cholesterol levels by approximately 9%.

Garlic as a lipid lowering agent--a meta-analysis.

Silagy C; Neil A
Department of Public Health and Primary Care, University of Oxford.
J R Coll Physicians Lond (England) Jan-Feb 1994, 28 (1) p39-45

Garlic supplements may have an important role to play in the treatment of hypercholesterolaemia. To determine the effect of garlic on serum lipids and lipoproteins relative to placebo and other lipid lowering agents, a systematic review, including meta-analysis, was undertaken of published and unpublished randomised controlled trials of garlic preparations of at least four weeks' duration. Studies were identified by a search of MEDLINE and the ALTERNATIVE MEDICINE electronic databases, from references listed in primary and review articles, and through direct contact with garlic manufacturers. Sixteen trials, with data from 952 subjects, were included in the analyses. Many of the trials had methodological shortcomings. The pooled mean difference in the absolute change (from baseline to final measurement in mmol/l) of total serum cholesterol, triglycerides, and high-density lipoprotein (HDL)- cholesterol was compared between subjects treated with garlic therapy against those treated with placebo or other agents. The mean difference in reduction of total cholesterol between garlic-treated subjects and those receiving placebo (or avoiding garlic in their diet) was -0.77 mmol/l (95% CI: -0.65, -0.89 mmol/l). These changes represent a 12% reduction with garlic therapy beyond the final levels achieved with placebo alone. The reduction was evident after one month of therapy and persisted for at least six months. In the dried garlic powders, in which the allicin content is standardised, there was no significant difference in the size of the reduction across the dose range of 600-900 mg daily. Dried garlic powder preparations also significantly lowered serum triglyceride by 0.31 mmol/l compared to placebo (95% CI: -0.14, -0.49).(ABSTRACT TRUNCATED AT 250 WORDS)

Limitation of the deterioration of lipid parameters by a standardized garlic - ginkgo combination product. A multicenter placebo-controlled double-blind study.

Kenzelmann R; Kade F
Institute for Clinical Research, Gumligen Switzerland.
Arzneimittelforschung (Germany) Sep 1993, 43 (9) p978-81

The efficacy of a garlic -ginkgo combination product (Allium plus) was analyzed in a randomized placebo-controlled double-blind study under extreme dietary conditions. The Christmas/New Year's season was chosen for this 2 months lasting investigation analyzing whether the known cholesterol lowering effect of garlic was even effective during the period of the year with the most cholesterol - rich meals. 43 patients with elevated total cholesterol levels ranging between 230-390 mg/dl completed the study. There were no significant changes of the total cholesterol values in both treatment groups. Nevertheless the analysis of improvement or deterioration of total cholesterol values revealed a clear difference between verum and placebo. 20% of the patients in the placebo group showed an improvement of their total cholesterol level, while there was a significant greater improvement rate of 35% in the verum group ($p < 0.05$). The responders of the verum group showed a reduction in the total cholesterol values from 298.5 ± 53.8 to 293.0 ± 56.4 mg/dl after 1 month and a total reduction of 10.4% after 2 months to 267.6 ± 44.4 mg/dl. The difference after 2 months of treatment was significantly different from the starting value ($p < 0.05$). After the 2 months treatment phase there was a 2 weeks wash-out period. During this period the total cholesterol value returned to 293.5 ± 90.1 mg/dl showing the effectiveness of garlic treatment, but indicating the need for a continuous long-term therapy.

Effect of garlic on total serum cholesterol. A meta-analysis

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Department of Medicine, New York Medical College, Valhalla 10595.

Ann Intern Med (United States) Oct 1 1993, 119 (7 Pt 1) p599-605

OBJECTIVE: To assess the size and consistency of garlic 's effect on total serum cholesterol in persons with cholesterol levels greater than 5.17 mmol/L (200 mg/dL).

DATA SOURCES: Clinical trials were identified by a computerized literature search of MEDLINE and by an assessment of the bibliographies of published studies and reviews.

STUDY SELECTION: Trials were selected if they were randomized and placebo-controlled and if at least 75% of their patients had cholesterol levels greater than 5.17 mmol/L (200 mg/dL). Studies were excluded if they did not provide enough data to compute effect size. Five of 28 studies were selected for review.

DATA EXTRACTION: Details of study design, patient characteristics, interventions, duration of therapy, and cholesterol measurements were extracted by one author and were verified by another.

DATA SYNTHESIS: Study quality was evaluated by multiple reviewers using a closed-ended questionnaire. Patients treated with garlic consistently showed a greater decrease in total cholesterol levels compared with those receiving placebo.

Meta-analysis of homogeneous trials estimated a net cholesterol decrease attributable to garlic of 0.59 mmol/L (95% CI, 0.44 to 0.74) (23 mg/dL [CI, 17 to 29]) (P < 0.001).

CONCLUSIONS: Meta-analysis of the controlled trials of garlic to reduce hypercholesterolemia showed a significant reduction in total cholesterol levels. The best available evidence suggests that garlic, in an amount approximating one half to one clove per day, decreased total serum cholesterol levels by about 9% in the groups of patients studied.

Effects of garlic coated tablets in peripheral arterial occlusive disease.

Kiesewetter H; Jung F; Jung EM; Blume J; Mrowietz C; Birk A; Koscielny J; Wenzel E

Abteilung für Klinische Hamostaseologie und Transfusionsmedizin, Universität des Saarlandes, Homburg/Saar.

Clin Investig (Germany) May 1993, 71 (5) p383-6

For the first time, a weak clinical efficacy of a 12-week therapy with garlic powder (daily dose, 800 mg) is demonstrated in patients with peripheral arterial occlusive disease stage II. The increase in walking distance in the verum group by 46 m (from 161.0 +/- 65.1 to 207.1 +/- 85.0 m) was significantly higher (P < 0.05) than in the placebo group (by 31 m, from 172.0 +/- 60.9 to 203.1 +/- 72.8). Both groups received physical therapy twice a week. The diastolic blood pressure, spontaneous thrombocyte aggregation, plasma viscosity, and cholesterol concentration also decreased significantly. Body weight was maintained. It is quite interesting that the garlic-specific increase in walking distance did not appear to occur until the 5th week of treatment, connected with a simultaneous decrease in spontaneous thrombocyte aggregation. Therefore, garlic may be an appropriate agent especially for the long-term treatment of an incipient intermittent claudication.

Can garlic reduce levels of serum lipids? A controlled clinical study.

Jain AK; Vargas R; Gotzkowsky S; McMahon FG

Clinical Research Center, New Orleans, Louisiana 70112.

Am J Med (United States) Jun 1993, 94 (6) p632-5

PURPOSE: To assess the effects of standardized garlic powder tablets on serum lipids and lipoproteins, glucose, and blood pressure.

SUBJECTS AND METHODS: Forty-two healthy adults (19 men, 23 women), mean age of 52 +/- 12 years, with a serum total cholesterol (TC) level of greater than or equal to 220 mg/dL received, in a randomized, double-blind fashion, either 300 mg three times a day of standardized garlic powder in tablet form or

placebo. Diets and physical activity were unchanged. This study was conducted in an outpatient, clinical research unit.

RESULTS: The baseline serum TC level of 262 +/- 34 mg/dL was reduced to 247 +/- 40 mg/dL ($p < 0.01$) after 12 weeks of standard garlic treatment. Corresponding values for placebo were 276 +/- 34 mg/dL before and 274 +/- 29 mg/dL after placebo treatment. Low-density lipoprotein cholesterol (LDL-C) was reduced by 11% by garlic treatment and 3% by placebo ($p < 0.05$). There were no significant changes in high-density lipoprotein cholesterol, triglycerides, serum glucose, blood pressure, and other monitored parameters.

CONCLUSIONS: Treatment with standardized garlic 900 mg/d produced a significantly greater reduction in serum TC and LDL-C than placebo. The garlic formulation was well tolerated without any odor problems.

Hypertension and hyperlipidaemia: garlic helps in mild cases.

Auer W; Eiber A; Hertkorn E; Hoehfeld E; Koehrl U; Lorenz A; Mader F; Merx W; Otto G; Schmid-Otto B; et al
Incorporated Society, Nittendorf, West Germany.
Br J Clin Pract Suppl (England) Aug 1990, 69 p3-6

Forty-seven non-hospitalised patients with mild hypertension took part in a randomised, placebo-controlled, double-blind trial conducted by 11 general practitioners. The patients who were admitted had diastolic blood pressures between 95 and 104 mmHg after a two-week acclimatization phase. The patients then took either a preparation of garlic powder (Kwai) or a placebo of identical appearance for 12 weeks. Blood pressure and plasma lipids were monitored during treatment after four, eight and 12 weeks. Significant differences between the placebo and the drug group were found during the course of therapy. For example, the supine diastolic blood pressure in the group having garlic treatment fell from 102 to 91 mmHg after eight weeks (p less than 0.05) and to 89 mmHg after 12 weeks (p less than 0.01). The serum cholesterol and triglycerides were also significantly reduced after eight and 12 weeks of treatment. In the placebo group, on the other hand, no significant changes occurred.

Therapy with garlic: results of a placebo-controlled, double-blind study.

Vorberg G; Schneider B
University of Hannover, West Germany.
Br J Clin Pract Suppl (England) Aug 1990, 69 p7-11

A double-blind study of 40 hypercholesterolaemic out-patients was carried out over a period of four months to examine the effects of a garlic powder preparation*. The drug group received 900 mg garlic powder per day, equivalent

to 2,700 mg of fresh garlic . During the therapy, the drug group showed significantly lower total cholesterol, triglycerides and blood pressure than those of the placebo group. In addition, results of a self-evaluation questionnaire indicated that patients in the drug group had a greater feeling of 'well-being'.

The effect of a garlic preparation on the composition of plasma lipoproteins and erythrocyte membranes in geriatric subjects.

Brosche T; Platt D; Dorner H

Chair of Internal Medicine-Gerontology, University of Erlangen-Nuremberg, West Germany.

Br J Clin Pract Suppl (England) Aug 1990, 69 p12-9

This study evaluated the effect of a dried garlic powder preparation, standardised to 1.3% alliin, on the composition of plasma lipoproteins and erythrocyte membranes. Forty volunteers, aged 70 years and over, took 600 mg of garlic powder per day for three months. In participants with initially normal plasma cholesterol levels (CH less than 200 mg/dl; n = 11) after three months of garlic tablet administration, little or no change in CH values was registered, as for most of the other parameters. In contrast, in volunteers with initially elevated CH levels (CH greater than 200 mg/dl, n = 29), the CH levels were reduced by -7.7% (p less than 0.001). This reduction took place primarily in the esterified cholesterol fraction (-12%, p less than 0.001), whereas free cholesterol concentrations were not altered significantly. Triglycerides (-15.9%, p less than 0.05) and plasma choline phospholipids (-4.6%, p less than 0.01) were also reduced. No change of the plasma LDL-CH to HDL-CH ratio was observed in this group. Based on the weight of lyophilised, haemoglobin-free erythrocytes, the mean membrane concentration of phospholipids and cholesterol in the total cohort (n = 40) increased by 5.7% (p less than 0.001) and 6.1% (p less than 0.01), respectively. These increases were more pronounced the lower the body mass indices (kg/m²) were, and the longer the duration of garlic administration was. The molar ratio of membrane phospholipids to cholesterol remained unchanged. The results are discussed with regard to a possible role of the garlic -induced membrane effects in the plasma lipid-lowering potency of garlic and preparations made from it.

Comparison of the efficacy and tolerance of a garlic preparation vs. bezafibrate.

Holzgartner H; Schmidt U; Kuhn U

Arbeits- und Forschungsgemeinschaft für Arzneimittel-Sicherheit e.V., Cologne, Fed. Rep. of Germany.

Arzneimittelforschung (Germany) Dec 1992, 42 (12) p1473-7

The efficacy and tolerance of a garlic preparation (Sapex, Kwai) was investigated in a randomized double-blind study vs. bezafibrate. This multi-centre study was

conducted in 5 general medical practices and involved 98 patients with primary hyperlipoproteinaemia. The daily doses of the active substances were 900 mg of garlic powder (standardized as to 1.3% alliin) and 600 mg of bezafibrate, respectively. The pre-phase with placebo lasted 6 weeks, the treatment period covered 12 weeks. All patients were advised to observe a low-fat "step-1 diet" for the duration of the study. The 98 case report forms allowed the statistical evaluation of total cholesterol, HDL cholesterol and triglyceride levels for 94 patients, and of LDL cholesterol values for 92 patients. In the course of the treatment both study medications caused a statistically highly significant reduction in total cholesterol, in LDL cholesterol and triglycerides, and an increase in HDL cholesterol. However, there was no significant difference in the efficacies of both medication groups. Side effects were mentioned by 5 patients each in both treatment groups, none of which led to the withdrawal of the patients. Concerning the garlic preparation, there was no correlation between the perception of garlic odour and the influence on the cholesterol level.

[Postprandial lipemia under treatment with *Allium sativum*. Controlled double-blind study of subjects with reduced HDL2- cholesterol]

Rotzsch W; Richter V; Rassoul F; Walper A
Institut für Klinische Chemie und Laboratoriumsdiagnostik, Universität Leipzig.
Arzneimittelforschung (Germany) Oct 1992, 42 (10) p1223-7

Postprandial Lipaemia under Treatment with *Allium sativum*/Controlled double-blind study in healthy volunteers with reduced HDL2-cholesterol levels. The effectiveness of a standardized garlic powder preparation (Saptec, Kwai) on alimentary hypertriglyceridaemia after intake of a standardized fatty test meal containing 100 g butter was analyzed in a randomized placebo-controlled double-blind study. 24 volunteers with HDL2- cholesterol concentrations in plasma of less than 10 mg/dl (men) respectively 15 mg/dl (women) participated in the study. The volunteers received 3 times 1 tablet daily over a period of 6 weeks equivalent to a daily dosage of 900 mg garlic powder in the active treated group. Control measurements were made on the 1st, 22nd and 43rd day of treatment and 0, 3 and 5 h after intake of the meal. The postprandial increase of triglycerides was clearly reduced under garlic medication as compared to placebo treatment. The determined AUC-values for the triglycerides were up to 35% lower in the garlic group compared to the placebo group. The regular intake of the garlic preparation over the period of 6 weeks showed a significant lowering of the fasting values of triglycerides in comparison to placebo. Under garlic medication HDL2-cholesterol increased more than under placebo in tendency.

Effect of ingestion of raw garlic on serum cholesterol level, clotting time and fibrinolytic activity in normal subjects.

Gadkari JV; Joshi VD

Department of Physiology, L. T. M. Medical College, Sion, Bombay, Maharashtra.

J Postgrad Med (India) Jul 1991, 37 (3) p128-31

The effect of raw garlic on serum cholesterol, fibrinolytic activity and clotting time was studied in 50 medical students of the age group of 17 to 22 years before and after feeding raw garlic. All pre-experimental values ranged within normal limits. The volunteers were then divided into experimental and control groups. The subjects of the experimental group were given 10 gm of raw garlic daily after breakfast for two months. Fasting blood samples of all the subjects were investigated after two months. In the control group, there was no significant change in any of the above parameters. In the experimental group, there was a significant decrease in serum cholesterol and an increase in clotting time and fibrinolytic activity. Hence, garlic may be an useful agent in prevention of thromboembolic phenomenon.

Effect of garlic on thrombocyte aggregation, microcirculation, and other risk factors.

Kiesewetter H; Jung F; Pindur G; Jung EM; Mrowietz C; Wenzel E

Department of Clinical Hemostasiology and Transfusion Medicine, University of the Saarland, Homburg.

Int J Clin Pharmacol Ther Toxicol (Germany) Apr 1991, 29 (4) p151-5

Significant positive effects could be achieved in a placebo-controlled double-blind study through the administration of 800 mg of garlic powder over a period of four weeks. Spontaneous thrombocyte aggregation disappeared, the microcirculation of the skin increased by 47.6% (from 0.63 +/- 0.13 to 0.93 +/- 0.22 mm/s), plasma viscosity decreased by 3.2% (from 1.25 +/- 0.34 to 1.21 +/- 0.43 mPas), diastolic blood pressure by 9.5% (from 74 +/- 9 to 67 +/- 5 mmHg), and blood glucose concentration by 11.6% (from 89.4 +/- 8.8 to 79.0 +/- 11.9 mg/dl). The vascular protection of garlic as atherosclerosis prevention by influencing the mentioned risk parameters for cardiovascular diseases must be pointed out. Especially interesting is the thrombocyte aggregation inhibiting effect. Thus, the application of garlic may be useful in case of acetylsalicylic acid intolerance.

[Garlic as phyto-genic antilipemic agent. Recent studies with a standardized dry garlic powder substance]

Brosche T; Platt D

Lehrstuhl für Innere Medizin-Gerontologie, Universität Erlangen-Nürnberg.

Fortschr Med (Germany) Dec 20 1990, 108 (36) p703-6

Garlic (*Allium sativum* L.) is a commonplace drug. It is now available in the form of dragees made of garlic powder, standardized to 1.3% alliin. The lipid-lowering potential of such preparations has not been reviewed yet. In 7 out of 8 studies, including over 500 patients, a daily dose of 0.6 g to 0.9 g garlic powder reduced plasma cholesterol and triglyceride levels by 5 to 20 percent. The metabolic mechanisms of these reductions are not known. (0 Refs.)

Treatment of hyperlipidaemia with garlic-powder tablets. Evidence from the German Association of General Practitioners' multicentric placebo-controlled double-blind study.

Mader FH

Study Group on Phytotherapy of the German Association of General Practitioners, Nittendorf.

Arzneimittelforschung (Germany) Oct 1990, 40 (10) p1111-6

In a multicentric placebo-controlled randomised study the effect of standardized garlic -powder tablets (Kwai, Sapec) in the treatment of hyperlipidaemia was investigated. A total of 261 patients of 30 general practitioners in West Germany with total cholesterol and/or triglyceride values more than 200 mg/dl (mostly hyperlipoproteinaemia type II a/II b) took part in the study. Patients were randomly allocated to take tablets containing a total of 800 mg garlic powder (standardized to 1.3% of alliin content) daily or the same number of placebo tablets for 16 weeks (monthly controlled). 221 patients were used for statistical analysis of total cholesterol and 219 patients for the analysis of triglyceride values. Mean serum cholesterol levels dropped in the verum group from 266 to 235 mg/dl (i.e. 12%) during the 4 month treatment period, mean triglyceride values fell in the verum group from 226 to 188 mg/dl (i.e. 17%). The best cholesterol lowering effects were seen in the patients with initial total cholesterol values between 250-300 mg/dl. The difference between the verum and placebo group was highly significant (p less than 0.001). A mild garlic smell was observed in up to 21% of the verum group and up to 9% in the placebo group. Only one of the patients left the study for this reason. Standardized garlic tablets have been shown to be effective in the treatment of hyperlipidaemia by lowering total cholesterol values by an average of 12% and triglyceride values by an average of 17%.

Garlic, onions and cardiovascular risk factors. A review of the evidence from human experiments with emphasis on commercially available preparations

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Department of Epidemiology/Health Care Research, University of Limburg, Maastricht, The Netherlands.

Br J Clin Pharmacol (England) Nov 1989, 28 (5) p535-44

1. Claims for beneficial effects on cholesterol levels, fibrinolytic activity, and platelet aggregation are attributed both to fresh garlic and onions (or their extracts) and to commercially available preparations.
2. Regarding fresh garlic, the claims have been confirmed, but so far only at very high dosages.
3. For onions and commercially available supplements contradictory results have been reported.
4. All published trials showed severe methodological shortcomings. Some trials were not randomized and/or not blinded whilst this was possible, and in only one of every three studies more than 25 patients participated in each treatment group. In no trial was prognostic comparability of the treatment and the control groups ascertained. At the moment there is inadequate scientific justification for garlic supplementation. (39 Refs.)

Effect of dried garlic on blood coagulation, fibrinolysis, platelet aggregation and serum cholesterol levels in patients with hyperlipoproteinemia.

Harenberg J; Giese C; Zimmermann R

First Medical Department, Klinikum Mannheim, University of Heidelberg, F.R.G. Atherosclerosis (Netherlands) Dec 1988, 74 (3) p247-9

The effects of intake of dried garlic on blood coagulation, fibrinolysis, platelet aggregation, serum cholesterol levels, and blood pressure were studied in 20 patients with hyperlipoproteinemia over a period of four weeks. Fibrinogen and fibrinopeptide A significantly decreased by 10%. Streptokinase activated plasminogen and fibrinopeptide B beta 15-42 significantly increased by about 10%. Serum cholesterol levels significantly decreased by 10%. Systolic and diastolic blood pressure decreased. ADP and collagen induced platelet aggregation were not influenced.

Lack of efficacy of dried garlic in patients with hyperlipoproteinemia.

Luley C; Lehmann-Leo W; Moller B; Martin T; Schwartzkopff W

Arzneimittelforschung (Germany, West) Apr 1986, 36 (4) p766-8

The effects of dried garlic on blood lipids, apolipoproteins and blood coagulation parameters in hyperlipemic patients were studied in two controlled, randomized, double-blind studies. Both studies comprised placebo and therapy periods of 6 weeks each. The doses administered were 3 X 198 mg in Study I (34 patients) and 3 X 450 mg in Study II (51 patients). In both studies, the following serum parameters were measured every 3 weeks: total cholesterol, HDL (high density lipoprotein)- and LDL (low density lipoprotein)- cholesterol, triglycerides and

several safety parameters. In addition, apolipoproteins A and B, euglobulin lysis time, fibrin split products, prothrombin time, whole blood coagulation time and fibrinogen levels were determined in the second study only. The results indicated that neither dosage of dried garlic showed any significant effect on any of the parameters measured. It is therefore concluded that, if there is any effect of garlic on the parameters measured, it is not apparent when using a dried preparation in the dosage studied.

Bulgarian traditional medicine: a source of ideas for phytopharmacological investigations.

Petkov V

J Ethnopharmacol (Switzerland) Feb 1986, 15 (2) p121-32

Some data about the use of medicinal plants in Bulgarian traditional medicine in the Middle Ages and in modern times are presented and the results of 40-year-long experimental-pharmacological investigations on many medicinal plants used in Bulgarian traditional medicine are reviewed. In-depth discussion is presented on the investigations of garlic (*Allium sativum* L.), a plant widely used by Bulgarian people for treating different diseases. Data from studies on a large number of plants used for treatment of hypertension, infectious diseases and as diuretic and spasmolytic remedies are summarized. (51 Refs.)

Influence of garlic on serum cholesterol, serum triglycerides, serum total lipids and serum glucose in human subjects.

Bakhsh R; Chughtai MI

Nahrung (Germany, East) 1984, 28 (2) p159-63

Human subjects were used for a garlic experiment. The subjects were given a fat-rich diet for 7 days and on the 8th day the fasting blood was analyzed for serum cholesterol, serum triglycerides, serum total lipids and serum glucose. The human subjects were then given a fat-rich diet with 40 g of garlic for 7 days and on the 15th day the fasting blood was analyzed for the above investigations. On a fat-rich diet the serum cholesterol, serum triglycerides and serum total lipids were significantly increased as compared to normally fed diet. When 40 g of garlic was substituted in fat-rich diet for 7 days, the garlic significantly reduced the serum cholesterol and serum triglycerides.

[Garlic therapy? Theories of a folk remedy (author's transl)]

Ernst E

MMW Munch Med Wochenschr (Germany, West) Oct 9 1981, 123 (41) p1537-8

Garlic has had a firm place in folk medicine since ancient times. More recent results are summarized here which show that extracts of the plant have an antimicrobial action, they are capable of lowering blood cholesterol and of reducing secondary vascular changes. They raise fibrinolytic activity and inhibit thrombocyte aggregation. Therefore the plant contains highly active therapeutic principles which appear to be particularly suitable for prophylaxis of arteriosclerosis.

The structure-hemolysis relationship of oleanolic acid derivatives and inhibition of the saponin-induced hemolysis with saponinins.

Hase J; Kobashi K; Mitsui K; Namba T; Yoshizaki M; Tomimori T
J Pharmacobiodyn (Japan) Nov 1981, 4 (11) p833-7

Chikusetsusaponin IV and V, whose genin is oleanolic acid, exhibited weak hemolytic activities. Removal of glucose residue at position 29 of chikusetsusaponin V by partial hydrolysis increased the activity more than 30-fold. Methylation of the carboxyl group at position 28 increased the activity furthermore by about 10-fold, showing HD50 value of 3.77 microM. On the other hand, removal of the sugar chain at position 3 of chickusetsusaponin V by partial hydrolysis completely lost the activity. These facts suggest that the sugar chain at position 3 of oleanolic acid is essential but that at position 29 is pernicious for the activity. The cytolytic agents, whose target has been regarded as membrane cholesterol, were inactivated not only by cholesterol but also by saponinins such as oleanolic acid, gitogenin and hederagenin. Among saponinins tested, akebia saponin B and C were inactivated by cholesterol, but not by the genins, probably because their affinities for the genins are too low to form complexes.

The long-term use of garlic in ischemic heart disease--an appraisal.

Arora RC; Arora S; Gupta RK
Atherosclerosis (Netherlands) Oct 1981, 40 (2) p175-9

The hypocholesterolemic and fibrinolysis-enhancing properties of garlic were assessed in patients with ischemic heart disease (IHD) and in healthy control subjects. The peak of blood fibrinolytic activity (BFA) achieved at the 4th week of garlic therapy was not sustained despite its continuous use and returned to about the pre-garlic values at the 12th week. Garlic withdrawal did not cause any further change in BFA. Under the same conditions serum total cholesterol (STC) values did not show any significant change. Both of the foregoing features were observed in the IHD as well as in the control group. Garlic therapy for 12 weeks did not cause any appreciable changes in serum triglyceride, beta-lipoprotein, plasma fibrinogen levels or coagulation time in either IHD or control subjects. The evidence cited above does not appear to substantiate the prevalent popular

belief in the efficacy of garlic in the management of IHD either as a hypocholesterolemic or as a fibrinolytic agent.

Comparative effect of clofibrate, garlic and onion on alimentary hyperlipemia.

Arora RC; Arora S

Atherosclerosis (Netherlands) Jul 1981, 39 (4) p447-52

The effect of clofibrate on the same subjects in similar test conditions were used as a control to verify the alleged beneficial effects from garlic and onion on alimentary hyperlipemia in normals and in cases with ischemic heart disease. The results showed that clofibrate checked the fat-induced (a) rises of serum triglyceride and plasma fibrinogen, and (b) falls of coagulation time (CT) and blood fibrinolytic activity (BFA). Only garlic had a clofibrate-like effect on CT but both garlic and onion checked the postprandial fall of BFA. Clofibrate, however, increased BFA even above the fasting level. Serum cholesterol and beta-lipoprotein were not appreciably affected by fat with or without any drug. Thus, surprisingly, the so-called beneficial effects of garlic and onion were not seen in subjects who had shown significant changes after clofibrate.

Effect of garlic on normal blood cholesterol level.

Bhushan S; Sharma SP; Singh SP; Agrawal S; Indrayan A; Seth P

Indian J Physiol Pharmacol (India) Jul-Sep 1979, 23 (3) p211-4

The effect of raw garlic on normal blood cholesterol level in males of the age group of 18-35 years was studied. The subjects, who never ingested garlic before, were given 10 g of garlic daily with their diet for two months. Fasting blood samples were investigated in respect of cholesterol before and after two months of garlic intake. Initially the blood cholesterol level ranged between 160-250 mg% which decreased significantly in all the subjects of experimental group after two months of ingestion of garlic. The slight decrease or increase in the blood cholesterol level of control group was not significant. The raw garlic can be advocated for daily ingestion in order to lower one's blood cholesterol level even if it is within normal limits.

Effect of the essential oils of garlic and onion on alimentary hyperlipemia.

Bordia A; Bansal HC; Arora SK; Singh SV

Atherosclerosis (Netherlands) Jan-Feb 1975, 21 (1) p15-9

Summary: The effect of garlic and onion on alimentary hyperlipemia, induced by feeding 100 g butter, has been studied in 10 healthy subjects. The freshly extracted juice of 50 g of garlic or onion, as well as an equivalent amount of their ether-extracted essential oils, was administered randomly on four different days during a one-week period. Garlic and onion have a significant protective action against fat-induced increases in serum cholesterol and plasma fibrinogen and decreases in coagulation time and fibrinolytic activity. The essential oil fraction, which contains all the taste and odour, exactly duplicated the beneficial effects of whole garlic and onion. It is, therefore, concluded that the active principle of garlic and onion is the essential oil, which chemically is a combination of sulphur-containing compounds, mainly allyl propyl disulphide and diallyl disulphide.

Garlic extract therapy in children with hypercholesterolemia

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Archives of Pediatrics and Adolescent Medicine (United States), 1998, 152/11 (1089-1094)

Objective: To determine whether garlic extract therapy is efficacious and safe in children with hypercholesterolemia.

Design: Randomized, double-blind, placebo-controlled clinical trial.

Setting: Specialized pediatric lipid disorders ambulatory clinic.

Participants: Thirty pediatric patients, aged 8 to 18 years, who had familial hyperlipidemia and a minimum fasting total cholesterol level greater than 4.8 mmol/L (>185 mg/dL).

Intervention: An 8-week course of a commercially available garlic extract (Kwai [Lichtwer Phanna, Berlin, Germany], 300 mg, 3 times a day) or an identical placebo.

Main Outcome Measures: Absolute and relative changes in fasting lipid profile parameters. Results: The groups were equivalent at baseline and compliance was similar in the 2 groups ($P = .45$). There was no significant relative attributable effect of garlic extract on fasting total cholesterol (+0.6% [95% confidence interval, -5.8% to +6.9%]) or low-density lipoprotein cholesterol (-0.5% [95% confidence interval, -8.7% to +7.6%]). The lower limits of the confidence intervals did not include -10%, the minimum relative attributable effect believed to be clinically important. Likewise, no significant effect was seen on the levels of high-density lipoprotein, triglycerides, apolipoprotein B-100, lipoprotein (a), fibrinogen, homocysteine, or blood pressure. There was a small effect on apolipoprotein A-I (+10.0% [95% confidence interval, +1.2% to +16.5%] $P=.03$). There were no differences in adverse effects between groups.

Conclusion: Garlic extract therapy has no significant effect on cardiovascular risk factors in pediatric patients with familial hyperlipidemia.

Changes in platelet function and susceptibility of lipoproteins to oxidation associated with administration of aged garlic extract

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Journal of Cardiovascular Pharmacology (United States), 1998, 31/6 (904-908)

Garlic and some of its organosulfur components have been found to be potent inhibitors of platelet aggregation in vitro. Demonstration of their efficacy in vivo, however, especially when administered over extended periods, is sparse. We recently performed a 10-month study comparing the effect of aged garlic extract (AGE) with placebo on the lipid profiles of moderately hypercholesterolemic men. In the course of the intervention trial, we examined platelet functions and susceptibility of lipoproteins to oxidation in a subgroup of this study population. Study subjects supplemented with 7.2 AGE per day showed a significant reduction of epinephrine- and, to a lesser degree, collagen-induced platelet aggregation but failed to demonstrate an inhibition of adenosine diphosphate (ADP)-induced aggregation. Platelet adhesion to fibrinogen, measured in a laminar flow chamber at moderately high shear rate, was reduced by similar 30% in subjects taking AGE compared with placebo supplement. A trend toward decreased susceptibility of lipoproteins to oxidation also was noted during AGE administration compared with the placebo period. We conclude that the beneficial effect of garlic preparations on lipids and blood pressure extends also to platelet function, thus providing a wider potential protection of the cardiovascular system.

Dietary therapy for preventing and treating coronary artery disease

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American Family Physician (United States), 1998, 57/6 (1299-1306)

Nearly one half of Americans die of cardiovascular disease. The morbidity and mortality associated with coronary artery disease is strongly related to abnormal lipid levels, oxidation of lipids and intra-arterial clot formation. Nutrition powerfully influences each of these factors. There is growing evidence that patients can improve lipid levels and decrease the rate of cardiovascular events by 'adding' specific foods to their diets and switching from saturated and polyunsaturated to monounsaturated fats and n-3 fatty acids. Appropriate dietary changes decrease arteriosclerotic plaque formation, improve endothelial vasomotor dynamics, reduce oxidation of low-density lipoproteins and enhance

thrombolytic activity. Brief discussions between physicians and patients can influence patients' food choices. Changes in diet can reduce the premature mortality and morbidity associated with coronary artery disease.

Effect of garlic on some blood lipids and hmgcoa reductase activity

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Iranian Journal of Medical Sciences (Iran), 1996, 21/3-4 (141-146)

Triglyceride, total cholesterol, HDL cholesterol, LDL cholesterol, lipoprotein (a), free fatty acids and glucose levels were measured in the serum or plasma of 86 normal male human subjects, aged 25 to 50 years, before and after one month of garlic powder consumption (one 400 mg garlic tablet, 3 times daily). Levels of total cholesterol, LDL cholesterol and triglycerides were significantly decreased after garlic consumption (by 10.7%, 11.5% and 14.2% respectively, $p < 0.05$). Furthermore, this decrease was significantly greater ($p < 0.05$) for initial cholesterol levels of > 200 mg/dl and triglyceride levels of > 150 mg/dl (14.7% and 15% respectively), and less pronounced for cholesterol levels of less than or equal to 200 mg/dl and triglyceride levels of less than or equal to 150 mg/dl (7.3% and 6% respectively). The reduction in LDL cholesterol was also significantly greater ($p < 0.05$) for initial levels of > 135 mg/dl (16.7%) as compared with levels of less than or equal to 135 mg/dl (10.0%). No significant differences existed in the levels of glucose, free fatty acids, lipoprotein (a) and HDL cholesterol measured before and after consumption of garlic. Measurements of cholesterol and triglycerides were also carried out in 15 normal male rats, weighing 250 to 300g, after receiving a diet containing 2.5% garlic powder for 10 days. Total cholesterol and triglyceride levels were significantly lower ($p < 0.05$) in these rats as compared to a control group receiving regular stock powder without garlic. The specific activity of HMGCoA reductase in the liver microsomal fraction of 12 normal male rats receiving the garlic powder (2.5% of the diet) for 10 days, was also significantly decreased ($p < 0.05$) as compared to a control group on the stock diet without garlic.

Physical performance support with combined phytotherapy. Ginseng, whitethorn and mixed pollen combination against stress

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Therapiewoche (Germany), 1996, 46/25 (1421-1425)

In a randomized, double-blind, clinically-controlled study, BNK 04, a combination of active ingredients containing ginseng, hawthorn, and micronized mixed pollen as its main ingredients, was administered to 18 stressed and

untrained patients (test group: 9 female, 9 male subjects; mean age = 56,9 years) for 40 days (first treatment phase). A significant increase in physical performance ($p < 103$) as compared to the control group (10 female, 8 male patients; mean age = 59,2 years) was detected by means of bicycle ergometry. The difference between groups was 20,0%, expressed as the Watt-minute product ($\Delta = 207 \text{ W} \times \text{min}$). Sixteen patients of the test group underwent a second treatment phase with BNK 04 (single-blind) following a 4-week washout phase, during which patients received placebo. At the onset of the second treatment phase, physical performance continued to be significantly increased ($p = 0,008$) compared to baseline (11,7%). At the end of treatment, the enhancement of physical performance was 20,6% compared to baseline ($p = 0,006$). Adverse drug reactions were not observed. These results demonstrate the conditioning effect on physical performance of the active ingredient combination, BNK 04, upon repeated administration.

Antioxidant of the coronary diet and disease

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Clinica Cardiovascular (Spain), 1996, 14/2 (29-38)

High levels of cholesterol and Low Density Lipoproteins (LDL) in plasma are related to high risk to develop Coronary Heart Disease (CHD). LDL-cholesterol is a primary ingredient of the atherosclerotic plaque; its accumulation in the subendothelial space is due to peroxidative reactions. Natural antioxidants such as carotenes, polyphenolic flavonoids, vitamin E and C show defensive properties against lipid peroxidation, hence it is possible to apply these molecules in clinical therapy in the prevention of the CHD. On the other hand, alcohol, and special red wine, as well as the intake of selenium can afford a cardioprotective effect. Blood cholesterol reduction, dietary and/or due to pharmacological interventions, could modulate lipid peroxidation through a decreased production of O_2^- , pivotal step in the peroxidative chain of reactions. The importance of other dietary components (fresh fruits, nuts, garlic and other vegetables as well as olive oil) have been analyzed to assess its influence and protective action in the prevention of CHD.

Satellite symposium 'International Garlic Research'

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Zeitschrift fur Phytotherapie (Germany), 1996, 17/1 (13-25)

The reports of the satellite symposium 'International Garlic Research' presented recent results of garlic research. Pharmacological investigations showed that the

vessel-dilatating effect of garlic powder extracts, allicin and ajoen is mediated by opening K⁺-channels and by membrane hyperpolarization. It could be shown that garlic powder directly affects cholesterol -accumulation by LDL and that there exists an inverse correlation between LDL-atherogenicity and sialic acid content of LDL. By garlic powder in hyperlipidemic patients the decreased sialic acid level could be normalized. Garlic constituents influence cholesterol biosynthesis on several levels. With respect to the late steps of cholesterol biosynthesis the inhibition of lanosterol 14-demethylase by allicin and ajoene was most important. Garlic also influences nitric oxide metabolism by increasing the blood levels of NO. Insufficient synthesis of NO in the blood may result in hypertension, angina pectoris and impotentia. A metaanalysis of clinical trials with garlic powder preparations proves their effects on blood pressure and lipid levels. A comparative trial of the effects of garlic powder and garlic oil has shown, that powder preparations have a stronger lipid-lowering effect than oil-preparations, while blood pressure is affected by powder preparations only. Another study showed that supplementation of a fish oil medication with garlic abolishes the fish-oil-induced increase of LDL-cholesterol levels and lowers the LDL-cholesterol levels. Finally the preliminary evaluation of an epidemiological study indicates that there are hints of a decreased stiffness of the aorta in humans with regular intake of a garlic powder preparation while another trial reveals a significant reduction of the extent of atheromatous plaques by garlic powder.

Garlic in hyperlipidemia. Influence of a garlic preparation on the lipid serum levels of patients with primary hyperlipidaemia

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Zeitschrift fur Phytotherapie (Germany), 1995, 16/6 (343-348)

The lipid lowering effect of an enteric coated garlic /cyclodextrine preparation (Tegra (R)) was investigated. 97 patients with known primary hyperlipidaemia (serum levels of total cholesterol exceeding 260 mg/100 ml) took part in this trial. Patients received 10 mg/day of essential garlic oil obtained by steam distillation of garlic . The trial was carried out of 3 months and for 6 months in those cases in which the aim of the treatment (reduction of serum levels of total cholesterol to values less than 260 mg/100 ml) had not been reached after 3 months. Most of the patients did not alter their diet, though they were advised to do so. In 28 of 97 patients the treatment was successful after 3 months. The total cholesterol (TC) decreased by 7.8% from 287 to 264 mg/100 ml in the mean, the triglycerides (TG) by 2.2% from 205 to 180 mg/100 ml, the low-density lipoprotein cholesterol (LDL-C) by 10.2% from 207 to 186 mg/100 ml. The high-density lipoprotein cholesterol (HDL-C) increased by 10% from 38.8 to 42.6 mg/100 ml. Continuing the trial for a further three months in 69 patients resulted in an overall reduction of TC by 14.1% to 246 mg/100 ml, of TG by 20.2% to 164 mg/100 ml, and of LDL-C by 18.8% to 168 mg/100 ml. HDL-C values in the same time increased by 17.6% to 45.6 mg/100 ml. All changes were statistically significant ($p < 0.001$). The aim of the treatment was reached by 90% of the patients (87 of 97). All

patients had a reduction of TC, TG and LDL-C and an increase in HDL-C. No severe side effects were observed. The results of the study demonstrate the efficacy of essential garlic oil/beta-cyclodextrine complexes in the treatment of hyperlipidaemia.

Therapeutic actions of garlic constituents

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Medicinal Research Reviews (USA), 1996, 16/1 (111-124)

Most studies on garlic during the past 15 years have been primarily in the fields of cardiovascular and cancer research. Cardiovascular studies have been mainly related to atherosclerosis, where effects were examined on serum cholesterol, LDL, HDL, and triglycerides. Although the studies were not consistent in relation to the dosage, standardization of garlic preparations, and period of treatment, most findings suggest that garlic decreases cholesterol and triglycerides levels in patients with increased levels of these lipids. Lowering of serum lipids by garlic ingestion may decrease the atherosclerosis process. The other major beneficial effect of garlic is due to its antithrombotic actions. This field of garlic research has been extensively studied. Garlic extracts and several garlic constituents demonstrate significant antithrombotic actions both in vitro and in vivo systems. Allicin and adenosine are the most potent antiplatelet constituents of garlic because of their in vitro effects. Since both allicin and adenosine are rapidly metabolized in human blood and other tissues, it is doubtful that these compounds contribute to any antithrombotic actions in the body. In addition, ajoene also seems not to be an active antiplatelet principle, because it is not naturally present in garlic, garlic powders, or other commercial garlic preparations. Only a small amount of ajoene can be found in garlic oil-macerates; however, ajoene is being developed as a drug for treatment of thromboembolic disorders. Recent findings on the identification of potent enzyme inhibiting activities of adenosine deaminase and cyclic AMP phosphodiesterase in garlic extracts are interesting, and may have a significant role in the pharmacological actions in the body. Presence of such enzyme inhibitors in garlic may perhaps explain several clinical effects in the body, including the antithrombotic, vasodilatory, and anticancer actions. Epidemiological studies have suggested that garlic plays a significant role in the reduction of deaths caused by malignant diseases. This had led many investigators to examine garlic and garlic constituents for their antitumor and cytotoxic actions both in vitro and in laboratory animals. The data from these investigations suggest that garlic contains several potentially important agents that possess antitumor and anticarcinogenic properties. In summary, the epidemiological, clinical, and laboratory data have proved that garlic contains many biologically and pharmacologically important compounds, which are beneficial to human health from cardiovascular, neoplastic, and several other diseases. Numerous studies are in progress all over the world to develop effective

and odorless garlic preparations, as well as to isolate the active principles that may be therapeutically useful.

Towards the control of the hypertension epidemic. The Philippine experience

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Philippine Journal of Internal Medicine (Philippines), 1995, 33/2 (33-35)

As of 1990 the Philippines is 2nd to Indonesia in hypertensive-related mortality. To reverse this trend, hypertension control strategies involve health provider and client perceptions of the issues. A recent Philippine Society of Hypertension (PSH) survey which included pooled historical data of 25,427 respondents showed 15% clinical practice hypertension prevalence. Most initial work-up includes ECG, urinalysis, cholesterol and sugar blood levels and chest x-ray examinations. Antihypertensive monotherapy preferences were calcium antagonists (25%), betablockers (8%), and diuretics (7%). Client awareness of being hypertensive is 52% with only 23% admitting good BP control. Almost 60% are asymptomatic at hypertension discovery. Role of diabetes, pregnancy, renal and eye problems in hypertension obtained low perception. Use of garlic and cleansing diet were perceived to be beneficial in BP control despite lack of documentation. Antihypertensive medication compliance was 33% in industrial patients compared to 51% in the general population. From this pooled survey data, programs and strategies will emerge in order to control the hypertension epidemic. A clear message seems obvious - it is wrong to assume that a patient understands a doctor's explanation readily.

How does garlic exert its hypocholesterolaemic action? The tellurium hypothesis

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Medical Hypotheses (United Kingdom), 1995, 44/4 (295-297)

The efficacy of garlic as a lipid-lowering agent is being increasingly recognized, but the biochemical mechanisms underlying this action are currently unknown. It is proposed that organic tellurium compounds, which are found in high concentration in fresh garlic buds, may contribute to this action by inhibiting squalene epoxidase, the penultimate enzyme in the synthetic pathway of cholesterol. Weanling rats fed a diet rich in tellurium develop a demyelinating polyneuropathy due to inhibition of this enzyme in peripheral nerves. Chronic exposure to small amounts of tellurium found in garlic might reduce endogenous cholesterol production through inhibition of hepatic squalene epoxidase and so reduce cholesterol levels. Tellurium may also contribute to the characteristic

odour of garlic since the most obvious clinical sign of tellurium poisoning is a garlic -like odour.

Efficacy of dietary recommendations and phytotherapy with *Allium sativum* in mild and moderate hypercholesterinemia

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Med. Welt (Germany), 1994, 45/7-8 (327-323)

Within a primary lipid screening including 9251 persons a group of 8001 subjects (65% women, 35% men) with a serum level of 221 -300 mg/dl total cholesterol are recommended a diet with low fat and cholesterol content during 6-8 weeks. The 'nonresponder' received by continuous diet 600 mg/die of *Allium sativum*. After the period with diet alone the mean serum cholesterol level decrease was 3 mg/dl, after the next weeks with additional application of garlic powder a decrease of 6 mg/dl was measured. Short time dietary recommendations alone are not as succesful as a diet connected with application of standardized garlic powder. With a good compliance the effect of diet on serum cholesterol level is supported by phytotherapy.

Effect of garlic powder tablets on blood lipids and blood pressure - A six month placebo controlled, double blind study

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Br. J. Clin. Res. (United Kingdom), 1993, 4/- (37-44)

In a double blind, placebo controlled randomised study the effects of a standardised garlic powder tablet (Kwai*), Lichtwer Pharma) on blood lipids and blood pressure was investigated. A total of 52 out-patients with total cholesterol values over 6.5 mmol/l took part in the study. Patients were randomly allocated to take tablets containing a total of 900 mg garlic powder (standardised to 1.3% alliin) daily or the same number of placebo tablets for six months. All patients were advised to follow a low fat/ cholesterol diet. Blood lipids were measured at baseline and after three and six months treatment. Blood pressure and well-being were assessed in monthly intervals. The baseline mean for serum total cholesterol of 6.92 mmol/l was reduced to 6.31 mmol/l after six months of garlic powder tablet treatment. Corresponding values for placebo were 7.05 mmol/l before and 6.74 mmol/l after placebo treatment. The difference between active treatment and placebo is statistically significant ($p < 0.05$). The mean values for low density lipoprotein cholesterol (LDL-C) was reduced by nearly 10% by garlic and by 6% by placebo. Mean systolic blood pressure (SBP) remained unchanged in the placebo group and was reduced in the active treated group by 17% from 145 to 120 mmHg ($p < 0.001$). Mean diastolic blood pressure (DBP) remained

unchanged in the placebo group and was reduced in the active treated group from 90 mmHg to 80 mmHg ($p < 0.01$). The differences between active and placebo treatment were significant after two months of treatment for DBP and after four months for SBP. Well-being, as analysed by a five-point score system, remained unchanged in the placebo group and was improved in the active treated group by 20% ($p < 0.001$).

Garlic supplementation and lipoprotein oxidation susceptibility

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Lipids (USA), 1993, 28/5 (475-477)

Interventions which make serum lipoproteins less susceptible to oxidation may be antiatherogenic. The antioxidant properties of garlic which have been demonstrated in vitro led us to investigate the effects of garlic supplements on lipoprotein oxidation susceptibility in humans. Ten healthy volunteers were given 600 mg/d of garlic powder (6 tablets of Kwai (R)) for two weeks in a placebo-controlled, randomized, double-blind crossover trial. We found that although serum lipid and lipoprotein levels were not lowered in this short time period, the ex vivo susceptibility of apolipoprotein B-containing lipoproteins to oxidation was significantly decreased (-34%). Because garlic has been reported to beneficially affect serum lipid levels, platelet function, fibrinolysis and blood pressure, this additional effect of retarding lipoprotein oxidation may contribute to the potential antiatherosclerotic effect of garlic .

Garlic as a phytogetic lipid-lowering drug - A review of clinical trails with standardized garlic powder preparations

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Fortschr. Med. (Germany, Federal Republic of), 1990, 108/36 (49-54)

Garlic (*Allium sativum* L.) is a commonplace drug. It is now available in the form of dragees made of garlic powder, standardized to 1.3% alliin. The lipid-lowering potential of such preparations has not been reviewed yet. In 7 out of 8 studies, including over 500 patients, a daily dose of 0.6 g to 0.9 g garlic powder reduced plasma cholesterol and triglyceride levels by 5 to 20 percent. The metabolic mechanisms of these reductions are not known.

Effect of an odor-modified garlic preparation on blood lipids

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Nutr. Res. (USA), 1987, 7/2 (139-149)

The effect of an odor-modified liquid garlic extract on blood lipids was evaluated in human subjects over a six month period. Lowering of cholesterol, triglycerides, low density and very low density lipoproteins (LDL, VLDL) with rise of high density lipoprotein (HDL) was observed in the majority of subjects who took garlic extract; the effect was clearly more significant than with subjects taking placebo. Garlic extract did not significantly influence the levels of cholesterol and triglycerides in subjects whose initial cholesterol levels were relatively low. Of special interest was the initial rise of cholesterol, triglycerides, and LDL/VLDL with garlic supplementation, suggesting possible mobilization of tissue lipids into the circulation during this phase of garlic ingestion. This study confirms previous reports of lowering cholesterol and triglycerides using various garlic preparations. Furthermore, it suggests that odor-modified garlic extract may be used in conjunction with dietary modification for control of hyperlipidemia.

Oral guar gum treatment of intrahepatic cholestasis and pruritus in pregnant women: effects on serum cholestanol and other non- cholesterol sterols.

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Eur J Clin Invest (England) May 1998, 28 (5) p359-63

BACKGROUND: Our aim was to investigate whether intestinal binding of bile acids by guar gum, a dietary fibre, relieves cholestasis and pruritus in intrahepatic cholestasis of pregnancy.

METHODS: Forty-eight pregnant women with cholestasis and pruritus were randomized double-blind to guar gum and placebo until the time of delivery, and 20 healthy pregnant women were used as control subjects. The pruritus score and serum bile acids, lipids and non-cholesterol sterols were measured at baseline, at least 2 weeks after treatment, just before delivery and up to 4 weeks after delivery.

RESULTS: The increase in serum bile acids and worsening of pruritus were prevented by guar gum in relation to placebo ($P < 0.05$). Serum cholesterol was unchanged, but increased cholesterol precursor sterol values suggested that cholesterol synthesis was increased by guar gum. Serum cholestanol proportion, an indicator of cholestasis, was related to pruritus but was unaffected by guar gum.

CONCLUSION: We conclude that in intrahepatic cholestasis of pregnancy and pruritus, guar gum treatment is beneficial in relieving pruritus, even although indicators of cholestasis are only partially reduced.

Increasing amounts of dietary fiber provided by foods normalizes physiologic response of the large bowel without altering calcium balance or fecal steroid excretion.

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Am J Clin Nutr (United States) Sep 1998, 68 (3) p615-22

Nine healthy, young men consumed constant diets to determine selected large-bowel, serum cholesterol and triacylglycerol, and calcium balance responses to 3 amounts of fiber provided by a mixture of fruit, vegetables, and grains. The diets, each consumed for 1 mo, contained 16, 30, and 42 g total fiber /d, of which 2.9, 4.8, and 7.7 g, respectively, was soluble. Mean daily wet and dry stool weights increased with each fiber addition. The first fiber addition increased defecation frequency and decreased fecal pH, bile acid concentration, and neutral steroid concentration; the second addition had no further effect. Mean weight of each defecation and stool moisture did not increase and serum cholesterol and triacylglycerol concentrations, calcium balance, and gastrointestinal transit time did not decrease as fiber intake increased. We conclude that 1) fiber provided by a mixed-food diet increases stool weight as effectively as does wheat or oat bran; 2) even high amounts of dietary fiber do not change transit time or defecation frequency if they are already approximately 1 and 2-3 d, respectively; 3) food patterns consistent with the food pyramid and incorporating legumes and whole grains are necessary to achieve recommended fiber intakes of 20-35 g/d, even if energy intake is > 12.55 MJ (3000 kcal); 4) soluble fiber provided by a mixture of whole foods has no effect on serum cholesterol concentrations or output of fecal bile acids; and 5) mixed-food fiber has little effect on calcium balance when calcium intakes are high (> or = 1.5 g/d).

[The use of dietary fiber as natural enterosorbents in diseases of the hepatobiliary system]

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Lik Sprava (Ukraine) Mar-Apr 1998, (2) p80-2

Intensity was studied of sorption of cholesterol, bile acids, and phospholipids by cereals food fibre in samples of vesicular and hepatic bile. Intensive absorption has been shown of these fractions by food fibres. Clinical observation over 92 patients with chronic noncalculous cholecystitis confirmed the beneficial effect of cereals food fibre.

Validity and reproducibility of a food frequency questionnaire to assess dietary intake of women living in Mexico City.

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Salud Publica Mex (Mexico) Mar-Apr 1998, 40 (2) p133-40

OBJECTIVE: To assess the reproducibility and validity of a 116 item semi-quantitative food frequency questionnaire (FFQ), designed to assess the relation between dietary intake and chronic diseases.

MATERIAL AND METHODS: To test the reproducibility of the FFQ questionnaire, the FFQ was administered twice to 134 women residing in Mexico City at an interval of approximately one year; to assess the validity we compared results obtained by the FFQs with those obtained by four 4-day 24-hour recalls at three month intervals. Validity and reproducibility were evaluated using regression analysis and Pearson and intraclass correlation coefficients of log-e and calorie-adjusted nutrient scores.

RESULTS: Mean values for intake of most nutrients assessed by the two food frequency questionnaires were similar. However, means for the 24-hr recall were significantly lower. Intraclass correlation coefficients for nutrient intakes, assessed by questionnaires, administered one year apart, ranged from 0.38 for cholesterol to 0.54 for crude fiber. Correlation coefficients between energy-adjusted nutrient intakes, measured by diet recalls, and the first FFQ ranged from 0.12 for polyunsaturated fatty acids to 0.67 for saturated fatty acids. Regression coefficients between 24-hr recall and FFQ,s were all significant were significant for all nutrients, except for polyunsaturated fat, folic acid, vitamin E and Zinc.

CONCLUSIONS: These data indicate that this semi-quantitative FFQ is reproducible and provides a useful estimate by which to categorize individuals by level of past nutrient intake. However, its application outside Mexico City or in different age and gender populations will require additional modifications and validation efforts.

Definition of healthy eating in the Spanish adult population: a national sample in a pan-European survey.

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Public Health (England) Mar 1998, 112 (2) p95-101

A national survey was carried out to find out how the Spanish adult population defined 'healthy eating'. Consumers were asked to describe in their own words what 'healthy eating' means to them. The sample included 1009 Spanish subjects over 15 y of age selected by a multistage procedure. This study belongs to the Spanish partnership in a pan-European survey about attitudes to food, nutrition and health coordinated by the Institute of European Food Studies of Dublin. The results were shown as the percentages of the sample who gave one of the five most frequently mentioned descriptions ('more vegetables', 'balanced diet', 'more fruit', 'less fat' and 'more fish') and the distribution of responses by age, sex, region, socio-economic level and education level. A multivariable logistic regression model was fitted to assess the characteristics independently related to the use of the definition 'balance and variety' for healthy eating. The majority of the Spanish people defined 'healthy eating' as a diet with 'more vegetables' as the main description. Other descriptions commonly mentioned were 'less fat', 'more fruit', 'more fish', and 'more lean meat'. A higher age was associated with a lower likelihood of mentioning the concept of balanced diet. A higher educational level was also independently and strongly related to a higher prevalence of this definition. Differences between men and women showed only borderline significance. Our results suggest the need to improve nutritional education about fiber, low fat and cholesterol. It would be interesting to develop strategies in Spain to educate people on a definition of 'healthy eating' based upon 'balance and variety'.

Zinc absorption, mineral balance, and blood lipids in women consuming controlled lactoovovegetarian and omnivorous diets for 8 wk.

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Am J Clin Nutr (United States) Mar 1998, 67 (3) p421-30

Zinc absorption, mineral balance, and blood lipid concentrations were measured in 21 women aged 33 +/- 7 y (range: 20-42 y) consuming controlled lactoovovegetarian and nonvegetarian diets for 8 wk each in a crossover design. The lactoovovegetarian and nonvegetarian diets, respectively, provided (by analysis) 973 and 995 mg Ca, 1.8 and 1.3 mg Cu, 367 and 260 mg Mg, 5.9 and 2.5 mg Mn, 1457 and 1667 mg P, 9.1 and 11.1 mg Zn, and (by calculation) 40 and 16 g dietary fiber, 2.5 and 0.8 mmol phytic acid, molar ratios of phytate to Zn of 14 and 5, and millimolar ratios of (phytate x Ca) to Zn of 344 and 111. Dietary zinc absorption was measured by extrinsic isotopic labeling and whole-body counting. Plasma cholesterol, cholesterol fractions, and lipoproteins were reduced 7-12% with the lactoovovegetarian diet, consistent with predictions based on dietary cholesterol and fat. Blood pressure was unaffected. Calcium, copper, magnesium, and phosphorus balances were not different between diets; manganese balance tended to be greater with the lactoovovegetarian diet ($P < 0.07$). The lactoovovegetarian diet was associated with a 21% reduction in absorptive efficiency that, together with a 14% reduction in dietary zinc, reduced

the amount of zinc absorbed by 35% (2.4 compared with 3.7 mg/d) and reduced plasma zinc by 5% within the normal range. Zinc balance was maintained with both diets. Although there is a greater risk of zinc deficiency in persons consuming lactoovovegetarian compared with omnivorous diets, with inclusion of whole grains and legumes zinc requirements can be met and zinc balance maintained.

Long-term effects of consuming foods containing psyllium seed husk on serum lipids in subjects with hypercholesterolemia.

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Am J Clin Nutr (United States) Mar 1998, 67 (3) p367-76

The effects of consuming foods containing 0 (control), 3.4, 6.8, or 10.2 g psyllium seed husk (PSH)/d for 24 wk on the serum lipid profile were assessed in this randomized, double-blind controlled study. Men and women (n = 286) with LDL-cholesterol concentrations between 3.36 and 5.68 mmol/L (130 and 220 mg/dL) were randomly assigned to one of four treatment groups after following a low-fat diet for > or = 8 wk. At week 24, LDL cholesterol was 3% above baseline in the control group. In the group consuming 10.2 g PSH/d, LDL cholesterol remained below baseline during treatment, with a value 5.3% below that of the control group at week 24 (P < 0.05 compared with the control group). No significant differences were observed in HDL cholesterol or triacylglycerol. Although modest, the effect of 10.2 g PSH/d on LDL cholesterol (relative to the control) persisted throughout the 24-wk treatment period, indicating potential for long-term benefit.

Decreased serum total cholesterol concentration is associated with high intake of soy products in Japanese men and women.

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J Nutr (United States) Feb 1998, 128 (2) p209-13

The relationship between soy product intake and serum total cholesterol concentration was examined in 1242 men and 3596 women who participated in an annual health check-up program in Takayama City, Japan, provided by the municipality in 1992. The intake of soy products and various foods and nutrients was assessed by a semiquantitative food-frequency questionnaire. Blood samples were collected from fasting subjects to measure the serum total cholesterol concentration. A significant trend (P for trend = 0.0001) was observed for

decreasing total cholesterol concentration with an increasing intake of soy products in men after controlling for age, smoking status and intake of total energy, total protein and total fat. This negative trend (P for trend = 0.0001) was also noted in women after controlling for age, menopausal status, body mass index and intake of total energy and vitamin C. An additional adjustment for physical activity, coffee and tea consumption, and intake of cholesterol, carbohydrates, fiber and vitamin E did not change the results. These data suggest a role for soy products in human cholesterol homeostasis.

Cholesterol, phospholipid, and protein changes in focal opacities in the human eye lens.

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Invest Ophthalmol Vis Sci (United States) Jan 1998, 39 (1) p94-103

PURPOSE: Focal opacities are signs of early cataractogenesis in the human lens. They progress slowly over a lifetime and may be precursors of mature cataracts. The authors analyzed changes in proteins, phospholipids, and cholesterol in these opacities using in situ techniques: Raman microspectroscopy, filipin cytochemistry for cholesterol, and transmission electron microscopy (TEM).

METHODS: Human lenses with verified focal opacities were fixed in 1% paraformaldehyde. Slabs with opacities were analyzed using confocal Raman spectroscopy, then filipin Raman analysis of cholesterol, and finally TEM.

RESULTS: Compared with normal fibers, opacities consistently showed elevated levels of cholesterol and aliphatic chains, increased phospholipid acyl chain disorder, and changes in phospholipid lateral packing. Disulfide bridges of specific geometry (trans-gauche-trans) were found. Although protein content was unchanged, compared with normal fibers, aromatic amino acid content was significantly lower. The hydrophobicity of tyrosine residues showed a significant decrease, and a change in the tryptophan indole ring angle was found. The changes were abrupt and sharply delineated focal opacities. TEM confirmed this sharp boundary and showed that the opacities were densely packed with vesicles of varying size and electron density embedded in a homogenous matrix.

CONCLUSIONS: The Raman and TEM analyses of opacities showed that early cataractogenic events led to disruption of fiber membranes, formation of vesicles from the membrane constituents, and protein changes. The aberrant morphology of the membranes enveloping the focal opacities may have segregated the affected fibers from the surrounding normal tissue, thus explaining the stationary or slowly progressing character of these opacities.

Food and nutrient intake of premenopausal female vegetarians and omnivores in Finland

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Scandinavian Journal of Nutrition/Naringsforskning (Sweden), 1998, 42/3 (98-103)

We have investigated the food and nutrient intake of five demi-vegans, six lacto-vegetarians and fourteen omnivores, all females and aged 22-45 years, collecting a total of 42 dietary records per person in 2-day periods during one year. The yearly mean intakes of cereals, vegetables, fruits and berries, dietary fibre and vitamin C were higher and that of sugar, eggs, saturated fat and cholesterol lower in the vegetarians than in the omnivores. The intake of iron was higher in the vegetarians, but their serum ferritin levels were lower throughout the year than in the omnivores indicating lower iron status in vegetarians. The vegetarian diets provided practically no vitamin D, which was reflected in a low serum 25-hydroxyvitamin-D concentration during spring, but during summer concentrations increased to the adequate level. Furthermore, the mean iodine intake of vegetarians using minor amounts of dairy products was below the recommended level. Thus, the vegetarians had lower cholesterol, saturated fat and higher carbohydrates and fibre intakes than omnivores. However, seven of the eleven vegetarians were iron deficient throughout the year and six had serum 25-hydroxyvitamin-D concentrations below reference values in the winter.

Functional food science and the cardiovascular system

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British Journal of Nutrition (United Kingdom), 1998, 80/Suppl. 1 (S113-S146)

Cardiovascular disease has a multifactorial aetiology, as is illustrated by the existence of numerous risk indicators, many of which can be influenced by dietary means. It should be recalled, however, that only after a cause-and-effect relationship has been established between the disease and a given risk indicator (called a risk factor in that case), can modifying this factor be expected to affect disease morbidity and mortality. In this paper, effects of diet on cardiovascular risk are reviewed, with special emphasis on modification of the plasma lipoprotein profile and of hypertension. In addition, dietary influences on arterial thrombotic processes, immunological interactions, insulin resistance and hyperhomocysteinaemia are discussed. Dietary lipids are able to affect lipoprotein metabolism in a significant way, thereby modifying the risk of cardiovascular disease. However, more research is required concerning the possible interactions

between the various dietary fatty acids, and between fatty acids and dietary cholesterol. In addition, more studies are needed with respect to the possible importance of the postprandial state. Although in the aetiology of hypertension the genetic component is definitely stronger than environmental factors, some benefit in terms of the development and coronary complications of atherosclerosis in hypertensive patients can be expected from fatty acids such as alpha-linolenic acid, eicosapentaenoic acid and docosahexaenoic acid. This particularly holds for those subjects where the hypertensive mechanism involves the formation of thromboxane A₂ and/or alpha₁-adrenergic activities. However, large-scale trials are required to test this contention. Certain aspects of blood platelet function, blood coagulability, and fibrinolytic activity are associated with cardiovascular risk, but causality has been insufficiently proven. Nonetheless, well-designed intervention studies should be initiated to further evaluate such promising dietary components as the various n-3 and n-6 fatty acids and their combination, antioxidants, fibre, etc. for their effect on processes participating in arterial thrombus formation. Long-chain polyenes of the n-3 family and antioxidants can modify the activity of immunocompetent cells, but we are at an early stage of examining the role of immune function on the development of atherosclerotic plaques. Actually, there is little, if any, evidence that dietary modulation of immune system responses of cells participating in atherogenesis exerts beneficial effects. Although it seems feasible to modulate insulin sensitivity and subsequent cardiovascular risk factors by decreasing the total amount of dietary fat and increasing the proportion of polyunsaturated fatty acids, additional studies on the efficacy of specific fatty acids, dietary fibre, and low-energy diets, as well as on the mechanisms involved are required to understand the real function of these dietary components. Finally, dietary supplements containing folate and vitamins B₆ and/or B₁₂ should be tested for their potential to reduce cardiovascular risk by lowering the plasma level of homocysteine.

Lipid- and glucose-lowering efficacy of Plantago Psyllium in type II diabetes

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Journal of Diabetes and its Complications (United States), 1998, 12/5 (273-278)

The beneficial effect of dietary fiber in the management of type II diabetes is still controversial and has not been totally demonstrated. The purpose of this study was to determine the plasma-lowering effects of 5 g t.i.d. of Plantago Psyllium, as an adjunct to dietary therapy, on lipid and glucose levels, in patients with type II diabetes. Patients were randomly selected from an outpatient clinic of primary care to participate in a double-blind placebo-controlled study in which Plantago Psyllium or placebo was given in combination with a low fat diet. One hundred twenty-five subjects were included in the study that consisted in a 6-week period of diet counseling followed by a 6-week treatment period. Fasting plasma glucose, total plasma cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels were measured every 2 weeks. The test products (Psyllium or placebo) were supplied to subjects in identically labeled foil packets containing a

5-g dose of product, to consume three doses per day (of 5 g each one), before regular meals. There was an excellent tolerance to Psyllium, without significant adverse effects. No significant changes were observed in the patient's weight for both groups (not significant). Fasting plasma glucose, total cholesterol, LDL cholesterol, and triglycerides levels, showed a significant reduction ($p < 0.05$), whereas HDL cholesterol increased significantly ($p < 0.01$) following Psyllium treatment. Our results show that 5 g t.i.d. of Psyllium is useful, as an adjunct to dietary therapy, in patients with type II diabetes, to reduce plasma lipid and glucose levels, resolving the compliance conflict associated with the ingest of a great amount of fiber in customary diet.

Whole flaxseed consumption lowers serum LDL- cholesterol and lipoprotein(a) concentrations in postmenopausal women

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Nutrition Research (United States), 1998, 18/7 (1203-1214)

We conducted a double-blind cross-over study to compare the effects of whole flaxseed and sunflower seed, as part of the daily diet, on the lipid profile of postmenopausal women. During two 6-wk periods, thirty-eight mild, moderate, or severely (5.85-9.05 mmol/L) hypercholesterolemic postmenopausal women were randomly assigned to one of the two regimens: flaxseed or sunflower seed. The subjects were provided with 38 g of either treatment in the forms of breads and muffins. The first treatment period lasted six weeks and was followed by a two-wk washout phase. After the washout phase, subjects switched regimens and treatments continued for another 6 weeks. Blood samples were collected at baseline, 6, 8, and 14th wk of the study periods. Significant ($p < 0.01$) reductions in total cholesterol were observed for both treatments (6.9 and 5.5% for flaxseed and sunflower seed, respectively). However only flaxseed regimen was able to significantly ($p < 0.001$) lower LDL- cholesterol (14.7%). Serum HDL- cholesterol and triglyceride concentrations were unaffected by either of the treatments. Most interestingly, lipoprotein(a) [Lp(a)], a strong predictor of cardiovascular disease, concentrations were significantly ($p < 0.05$) lowered by the flaxseed treatment (7.4% compared to baseline values). Regression analyses showed the strongest association between age and both total and LDL- cholesterol concentrations. Among the dietary variables, total and soluble fiber intakes were negatively correlated with serum total and LDL-cholesterol concentrations. The cholesterol lowering effects of flaxseed and sunflower seed may be due to the activity of single or multiple components, including alpha-linolenic or linoleic acids, total and soluble fiber, and non-protein constituents present in these seeds.

The potential role of soluble fibre in the treatment of hypercholesterolaemia

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Postgraduate Medical Journal (United Kingdom), 1998, 74/873 (391-394)

The three major modifiable coronary risk factors are smoking, hypertension, and hypercholesterolaemia. Serum cholesterol levels are above the desirable level of 5.2 mmol/l in 79% of men and 65% of women aged between 35 and 50 years and thus are an important target for intervention. In this paper, the role of nonpharmacological intervention with soluble fibre in treating mild to moderate primary hypercholesterolaemia is reviewed. Evidence from controlled studies shows that soluble fibre can be effective in lowering cholesterol by clinically significant amounts. It is stressed, however, that risk factors for coronary heart disease are interactive and attention is shifting to addressing multiple rather than individual factors.

Nutrition and coronary heart disease

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Comprehensive Therapy (United States), 1998, 24/4 (198-204)

Modification of the nutritional risk factors, along with moderate amount of fiber content in food, fresh fruits and vegetables, necessary mineral supplements, smoking reduction and routine physical exercise, is an important strategy for the prevention and reduction of adverse outcome in coronary heart disease.

Dietary fiber , the evolution of the human diet and coronary heart disease

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Nutrition Research (United States), 1998, 18/4 (633-652)

Speculation on the evolution of the human diet together with comparative studies with the diet of other primates suggest that the human gastrointestinal tract and metabolism are adapted to high fiber diets. Epidemiological studies support a negative association between dietary fiber intake and risk of coronary heart diseases (CHD). For the most part, the association has been with insoluble fiber , especially wheat bran. However, viscous fiber sources are likely to play a role since they reduce lipid risk factors for CHD including total and low-density-

lipoprotein cholesterol and apolipoprotein B by increasing fecal bile acid losses. In addition, soluble fiber may reduce the rate of nutrient absorption so altering chylomicron synthesis and reducing postprandial glucose and insulin levels and other risk factors for CHD. There is also evidence that some insoluble fibers might alter serum lipids and improve carbohydrate tolerance but these phenomena need to be confirmed and other mechanisms explored including improved clothing and thrombolytic factors and increased antioxidant status. Epidemiology, clinical and laboratory studies support increased consumption of high fiber foods as part of the strategy to reduce the risk of CHD.

Managing hypercholesterolaemia: What role for dietary fibre?

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British Journal of Cardiology (United Kingdom), 1998, 5/3 (156-163)

Although there is now general agreement that lowering blood cholesterol levels brings about a reduction in the incidence of coronary heart disease (CHD), there is no consensus as to how and on whom lipid lowering should be attempted. With millions of people likely to benefit from cholesterol lowering, many of them with no overt signs or symptoms of CHD, managing hypercholesterolaemia needs to be effective, inexpensive, and highly acceptable to patients. This review looks briefly at the need to manage hypercholesterolaemia, and then considers the methods available for management. In particular, it explores the potential role of the addition of soluble fibre to the diet.

Human fatty acid synthesis is reduced after the substitution of dietary starch for sugar

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American Journal of Clinical Nutrition (United States), 1998, 67/4 (631-639)

Using new nonisotopic and isotopic methods, we showed previously that fatty acid synthesis was markedly stimulated in weight-stable normal volunteers by a very-low-fat formula diet with 10% of energy as fat and 75% as short glucose polymers. In this study, we determined whether fatty acid synthesis was equally stimulated by a very-low-fat solid diet made with foods consumed typically. Four normal volunteers consumed the same very-low-fat formula diet for 25 d and then an isoenergetic solid food diet with 10% of energy as fat and 75% as starch, simple sugars, and fiber for 25 d. To measure fatty acid synthesis, the fatty acid compositions of the diets were matched to the composition of each subject's

adipose tissue and compared with the composition of VLDL-triacylglycerol. In all subjects, the large increases in newly formed palmitate and decreases in linoleate in VLDL-triacylglycerol were quickly reversed by the solid food diet, and the fraction of de novo synthesized fatty acids in fasting VLDL-triacylglycerol decreased from 30- 54% to 0-1%. In a second group of subjects, the stimulation of fatty acid synthesis by the formula diet with 75% glucose polymers was similarly reduced by a formula diet with amounts of fat, starch, and sugar chosen to mimic those of the solid food diet, but persisted after the addition of fiber or a diet with 75% sugar. In conclusion, an increase in fatty acid synthesis and palmitate-rich, linoleate-poor VLDL-triacylglycerol induced by very-low-fat, high-sugar diets may be reduced by the substitution of dietary starch for sugar with potentially beneficial effects on cardiovascular health.

Influence of vitamin C status on ethanol metabolism in guinea-pigs.

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Physiol Res (Czech Republic) 1998, 47 (2) p137-41

Guinea-pigs were maintained for 5 weeks on a diet containing three different concentrations of vitamin C : a) traces (none added), b) medium (0.05% w/w) and high (0.5% w/w). Twenty-four hours before killing the animals received one i.p. dose of 3 g ethanol per kg body weight (a model of short-term acute intoxication). In a parallel experiment which lasted 5 weeks, the animals were treated every week with two i.p. doses of 1 g ethanol per kg body weight followed by the final acute intoxication (3g ethanol/kg) (a model of long-term chronic alcoholization). In both experiments, the guinea-pigs with the highest tissue concentration of vitamin C proved to have significantly decreased residual levels of ethanol and acetaldehyde in the liver and the brain, a decreased activity of alanine- and aspartate aminoacyl transferases in the serum and decreased contents of triacylglycerols and cholesterol in the serum and liver in comparison with the vitamin C -unsupplemented group. The regression curve expressing vitamin C levels versus residual ethanol and acetaldehyde concentrations in the liver confirmed the highly significant negative correlation between them. Administration of the guinea-pigs with large amounts of vitamin C appears to accelerate ethanol and acetaldehyde metabolism and reduce some of their adverse health effects.

Dietary antioxidants inhibit development of fatty streak lesions in the LDL receptor-deficient mouse.

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Arterioscler Thromb Vasc Biol (United States) Sep 1998, 18 (9) p1506-13

Oxidized low density lipoprotein (LDL) promotes atherogenesis. Although pharmacological antioxidants such as probucol inhibit both LDL oxidation and atherosclerosis in hyperlipidemic animals, the effects of natural antioxidants such as vitamin E are inconclusive. To further determine the effects of supplemental dietary antioxidants in vivo, we evaluated whether combined dietary antioxidants (0.1% vitamin E, 0.5% beta-carotene, and 0.05% vitamin C) inhibit LDL oxidation and fatty streak lesion development in homozygous LDL receptor-null (LDLR^{-/-}) mice fed a high-fat, high- cholesterol diet. An additional group of mice were fed black tea, which has been shown to inhibit LDL oxidation in vitro. After receiving a high-fat, high- cholesterol diet for 8 weeks, the combined antioxidant-supplemented (antioxidant) group (n=18), tea group (n=19), and control group (n=17) had equivalent plasma cholesterol levels. LDL oxidation, as measured by the lag phase of conjugated diene formation, was markedly inhibited in the antioxidant group compared with the tea or control groups [mean lag phases=143±7 (antioxidant), 100±5 (tea), and 84±4 (control) minutes; P<0.0001 antioxidant versus tea or control]. The cross-sectional surface area of fatty streak lesions in the aortic sinus was reduced by 60% in the antioxidant group compared with both the tea and control groups (P<0.0001 antioxidant versus tea or control). There was no difference in lesion area between tea and control groups. Although both LDL oxidation and atherosclerosis were significantly inhibited in the antioxidant group, no correlation between lag phase values and lesion size was observed among individual animals. Furthermore, black tea did not inhibit fatty streak development in LDLR^{-/-} mice. These data suggest that combined natural dietary antioxidants inhibit both LDL oxidation and atherogenesis in animals with elevated LDL but that inhibition of LDL oxidation alone may not prevent the development of atherosclerosis.

Vitamin E combined with selenium inhibits atherosclerosis in hypercholesterolemic rabbits independently of effects on plasma cholesterol concentrations.

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Circ Res (United States) Aug 24 1998, 83 (4) p366-77

Several antioxidants inhibit atherosclerosis. This study investigated the hypothesis that combining vitamin E, a lipophilic antioxidant, with vitamin C, a hydrophilic antioxidant, and/or selenium, a cofactor of peroxidases that detoxify lipid peroxides, would inhibit atherosclerosis more effectively than vitamin E alone. We also considered whether regional variation in inhibition of atherosclerosis by antioxidants would be associated with regional variation in aortic lipophilic antioxidants. Rabbits were fed an atherogenic diet (control) or an atherogenic diet supplemented with vitamin E, vitamins E and C, vitamin E+selenium, vitamins E and C+selenium, or probucol (positive control). Supplements were as follows: vitamin E, 146 IU/d; vitamin C, 791 mg/d; selenium, 22 microg/d; or probucol,

406 mg/d. Vitamin C did not influence atherosclerosis. After 22 weeks of treatment, rank order of aortic atherosclerosis was control>vitamin E (with or without vitamin C)>vitamin E+selenium (with or without vitamin C)>probucol. Antioxidant treatment reduced aortic cholesterol concentrations 21% to 56%, 29% to 86%, and 19% to 75% for the aortic arch, descending thoracic aorta, and abdominal aorta, respectively ($P<0.025$ to $P<0.0003$ by ANOVA), with slightly greatly reductions for areas of atherosclerotic lesions. Some treatments reduced plasma cholesterol concentrations, but none altered the distribution of cholesterol among lipoproteins. Corrected for differences in plasma cholesterol concentrations, aortic cholesterol concentrations were reduced up to 72% ($P<0.02$) by the antioxidant treatments, with equal reductions by vitamin E+selenium and by probucol. Aortic alpha-tocopherol standardized by aortic cholesterol as a measure of aortic lipids was lower in the abdominal aorta than in the aortic arch of rabbits not given alpha-tocopherol and increased relatively more in the abdominal aorta than in the aortic arch with alpha-tocopherol supplementation. The results of this study suggest that vitamin E+ selenium inhibited atherosclerosis as effectively as an equally hypocholesterolemic dose of probucol by a mechanism(s) that is in part independent of effects on plasma and lipoprotein cholesterol concentrations. The tendency for greater efficacy of antioxidant treatments in the abdominal aorta than aortic arch may relate to the lower concentrations of alpha-tocopherol in the abdominal aorta of unsupplemented rabbits.

Regulation of apolipoprotein B-containing lipoproteins by vitamin C level and dietary fat saturation in guinea pigs.

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Metabolism (United States) Jul 1998, 47 (7) p883-91

Effects of suboptimal and adequate vitamin C, with varying dietary fat saturation, on hepatic cholesterol and plasma lipoprotein concentrations and metabolism were studied in guinea pigs fed 15% (wt/wt) fat/0.04% cholesterol diets. Fat mixtures were either 49% saturated (SFA) (24% lauric acid) or 53% polyunsaturated fatty acid (PUFA) linoleic acid with vitamin C at 50 (suboptimal) or 500 (adequate) mg/kg diet. Guinea pigs fed suboptimal vitamin C had 15% lower hepatic active 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase activity and 25% lower low-density lipoprotein (LDL; apolipoprotein [apo] B/E) receptor number, 20% higher acyl-CoA:cholesterol acyltransferase (ACAT) activity, 28% higher triacylglycerol (TAG) and cholesteryl ester concentrations, and increased very-low-density lipoprotein (VLDL) apo B secretion rates in comparison to animals fed adequate vitamin C. Intake of suboptimal vitamin C lowered plasma high-density lipoprotein (HDL) cholesterol concentrations by 45% and increased plasma TAG, total and VLDL/LDL cholesterol, and cholesteryl ester transfer protein (CETP) activity by 40%, 50%, and 30%, respectively. The hyperlipidemic effects of suboptimal vitamin C were

more pronounced with intake of the SFA diet. These data demonstrate that low vitamin C intake results in a pattern of changes in whole-body cholesterol and lipoprotein metabolism that are related to increased risk of cardiovascular disease (CVD).

The nutritional health of New Zealand vegetarian and non-vegetarian Seventh-day Adventists: selected vitamin, mineral and lipid levels.

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N Z Med J (New Zealand) Mar 27 1998, 111 (1062) p91-4

AIM: To determine whether adult non-vegetarian Seventh-day Adventists differ in selected nutrition related health aspects from adult vegetarian Seventh-day Adventists.

METHODS: One hundred and forty-one Seventh-day Adventist church members responded to a general health questionnaire. Forty-seven sex and age matched subjects (23 non-vegetarians and 24 vegetarians) were selected for further investigation. Blood lipids, serum vitamin B12, folate, haemoglobin and ferritin levels were measured along with stature, weight and blood pressure. A quantitative 7-day diet record was also completed.

RESULTS: Body mass index was similar between the non-vegetarian and vegetarian groups but diastolic blood pressure was higher for non-vegetarian than vegetarian males. Even though the dietary vitamin B12 intake was significantly lower ($p < 0.01$) in the vegetarian group both vegetarians and non-vegetarians recorded similar serum vitamin B12 levels. The vegetarian and non-vegetarian groups had similar haemoglobin concentrations. While dietary iron intake was higher in the female vegetarian group, though predominantly in the non-haem form, the difference was not significant. Low serum ferritin levels were found in both female dietary groups even though the vegetarian group had a significantly ($p < 0.05$) higher vitamin C intake. Blood lipid levels were similar in the two diet groups even though the vegetarian group had a lower percentage energy contribution from total and saturated fat ($p < 0.01$) and consumed significantly less cholesterol.

CONCLUSION: Both non-vegetarian and vegetarian Seventh-day Adventists appear likely to enjoy a lower risk of nutrition related chronic degenerative disease than the average New Zealander and have a satisfactory iron and vitamin B12 status.

Low-density lipoprotein oxidation and vitamins E and C in sustained and white-coat hypertension.

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Hypertension (United States) Feb 1998, 31 (2) p621-6

Low-density lipoprotein oxidation and antioxidant vitamins E and C were investigated in white-coat hypertension in comparison with sustained hypertension and normotension. We selected 21 sustained hypertensive subjects, 21 white-coat hypertensive subjects, and 21 normotensive subjects matched for gender, age, and body mass index. White-coat hypertension was defined as clinical hypertension and daytime ambulatory blood pressure <139/90 (subjects were also reclassified using 134/90 and 135/85 mm Hg as cutoff points for daytime blood pressure). Blood samples were drawn for lipid profile determination, assessment of fluorescent products of lipid peroxidation in native LDL, evaluation of susceptibility to LDL oxidation in vitro (lag phase and propagation rate), and determination of LDL vitamin E and plasma vitamins E and C contents. Compared with sustained hypertensive subjects, white-coat hypertensives had significantly lower fluorescent products of lipid peroxidation (15.4±3.4 versus 10.2±3 units of relative fluorescence/mg LDL protein, $P<.05$), longer lag phase (54±10 versus 88±10 minutes, $P<.05$), lower propagation rate (8.2±2.5 versus 5.95±2.1 nmol diene/min per mg LDL cholesterol, $P<.05$), higher LDL vitamin E content (8.3±1.1 versus 10.1±1.8 nmol/mg LDL cholesterol, $P<.05$), and plasma vitamin C content (40±13 versus 57±9 micromol/L, $P<.05$). No significant difference was observed between white-coat hypertensive and normotensive subjects. The results did not change after reclassification of subjects. Our data show that white-coat hypertensive subjects do not show an enhanced propensity to LDL oxidation or reduction in antioxidant vitamins. Given the role of LDL oxidation in the development of atherosclerosis and that of vitamin E and C in protecting against it, these findings suggest that white-coat hypertension per se carries a low atherogenic risk.

Citrus fruit supplementation reduces lipoprotein oxidation in young men ingesting a diet high in saturated fat: presumptive evidence for an interaction between vitamins C and E in vivo.

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Am J Clin Nutr (United States) Feb 1998, 67 (2) p240-5

To determine the effects of vitamin C on cardiovascular risk factors, we studied dietary vitamin C enrichment in 36 healthy male students consuming a diet high in saturated fatty acids. After a 1-mo run-in period during which the subjects consumed approximately 50 mg ascorbic acid/d (low-C diet), half of the subjects were randomly assigned to receive 500 mg ascorbic acid/d for an additional 2 mo (high-C diet). Plasma ascorbic acid increased from 13.5 micromol/L with the low-

C diet to 51.7 micromol/L with the high-C diet. Plasma cholesterol increased slightly with the high-C diet, but not above baseline concentrations. This increase was offset by an increase in the lag period of in vitro LDL oxidation, which correlated with plasma ascorbic acid concentrations ($r = 0.735$, $P = 0.0012$). Lipoprotein vitamin E concentrations were unchanged with the two diets. There were no effects on concentrations of fibrinogen or factor VII. The fact that ascorbic acid reduced the in vitro susceptibility of lipoproteins to oxidation provides presumptive evidence for an interaction between aqueous and lipophilic antioxidants (vitamins C and E) in maintaining the integrity of LDL particles.

Diet, antioxidant status, and smoking habits in French men

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Am J Clin Nutr (United States) Feb 1998, 67 (2) p231-9

The aim of this study was to assess the association between smoking, food consumption, and antioxidant vitamin intake and plasma indexes of oxidative stress and antioxidant defenses in French adults. Food and nutrient intakes of 459 healthy men aged 23-57 y were estimated by the diet history method and analyzed by smoking status. Plasma alpha-tocopherol, ascorbic acid, and carotenoids were measured as antioxidants and malondialdehyde, protein Schiff bases, and autoantibodies against malondialdehyde-protein adducts as oxidative stress indexes. Smokers ate less fruit and vegetables than nonsmokers, leading to lower vitamin E, vitamin C, and carotene intakes, even after adjustment for age, education, and marital status. Unlike vitamin E, plasma ascorbic acid and beta-carotene concentrations were reduced in smokers compared with nonsmokers and were inversely related to cigarette consumption. This difference remained significant after adjustment for alcohol and dietary intakes. Among the measured oxidative stress indexes, only Schiff base concentration was positively related to the number of cigarettes smoked. In our sample of French men, smoking had an adverse effect on antioxidant status; vitamin intakes were reduced in smokers and plasma antioxidant indexes were altered independently of dietary intakes. As in other countries, in France smokers require particular attention in terms of public health intervention.

Vitamin C supplementation restores the impaired vitamin E status of guinea pigs fed oxidized frying oil.

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J Nutr (United States) Jan 1998, 128 (1) p116-22

To investigate the effect of dietary oxidized frying oil (OFO) on tissue retention of vitamin C, and to explore the effect of vitamin C supplementation on tissue vitamin E concentrations and lipid peroxidation, male weanling guinea pigs were divided into four groups. Guinea pigs were fed 15% OFO diets supplemented with vitamin C at 300, 600 or 1500 mg/kg diet. Control animals were fed a diet containing 15% fresh untreated soybean oil with 300 mg/kg of vitamin C. After 60 d of feeding, body weight gain, food intake, feed efficiency and plasma triglyceride concentration were significantly lower in guinea pigs fed OFO diets than in controls ($P < 0.05$). However, plasma cholesterol concentration was highest in guinea pigs fed the OFO diet supplemented with 300 mg/kg vitamin C. Increasing vitamin C in OFO diets significantly reduced plasma cholesterol concentration. Plasma and tissue vitamins C and E concentrations were significantly lower in the OFO-fed guinea pigs receiving 300 mg/kg vitamin C than in controls. Greater levels of supplemental vitamin C increased tissue vitamins C and E. Guinea pigs fed OFO diets had significantly higher tissue levels of thiobarbituric acid reactive substances (TBARS) ($P < 0.05$) than controls. Our results demonstrated that OFO feeding, which impaired alpha-tocopherol retention and increased TBARS, could be alleviated somewhat by vitamin C supplementation.

Antioxidant vitamins and coronary artery disease risk in South African males

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Clinica Chimica Acta (Netherlands), 1998, 278/1 (55-60)

Decreased antioxidant-vitamin nutritional status may increase lipid peroxidation and susceptibility of low-density lipoprotein (LDL) to oxidative modification. The aim of this study was to evaluate the vitamin nutritional status of coronary artery disease (CAD) patients and to assess the risk of CAD related to each individual antioxidant vitamin. The study was performed as a case-control study with 41 patients with angiographically demonstrated CAD and 41 apparently healthy age- and smoking status-matched controls. Plasma vitamin E, C and A concentrations were significantly decreased in CAD patients compared with controls ($p < 0.001$) after correcting for significant covariates. Per quartile decrease in vitamin A and E concentrations was associated with increased risk of CAD, even after adjusting for CAD risk factors, while per quartile decrease in vitamin C concentrations was not associated with significant CAD risk after adjusting for CAD risk factors. Decreased vitamin A and E concentrations are independently associated with increased risk of CAD independent from other CAD risk factors in white male South Africans and dietary intervention strategies are advocated. Copyright (C) 1998 Elsevier Science B.V.

Vitamins E plus C and interacting conutrients required for optimal health

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BioFactors (Netherlands), 1998, 7/1-2 (113-174)

Antioxidants are crucial components of fruit/vegetable-rich diets preventing cardiovascular disease (CVD) and cancer: - plasma vitamins C, E, carotenoids from diet correlate prevalence of CVD and cancer inversely, low levels predict an increased risk of individuals which is potentiated by combined inadequacy (e.g., vitamins C+E, C+carotene, A+carotene); - self-prescribed rectification of vitamins C and E at adequacy of other micronutrients reduce forthcoming CVD, of vitamins A, C, E, carotene and conutrients also cancer; - randomized exclusive supplementation of beta-carotene plus or minus vitamin A or E lack benefits except prostate cancer reduction by vitamin E, and overall cancer reduction by selenium; - randomized intervention with synchronous rectification of vitamins A+C+E+B + minerals reduces CVD and counteracts precancerous lesions; - high vitamin E supplements reveal potentials in secondary CVD prevention. Plasma values desirable for primary prevention: less than or equal to 30 micromol/l lipid-standardized vitamin E alpha-tocopherol/cholesterol less than or equal to 5.0 micromol/mmol); less than or equal to 50 micromol/l vitamin C aiming at vitamin C /vitamin E ratio >1.3-1.5; less than or equal to 0.4 micromol/l beta- (less than or equal to 0.5 micromol/l alpha+beta-) carotene. Conclusions: - in CVD vitamin E acts as first risk discriminator, vitamin C as second one; - optimal health requires synchronously optimized vitamins C+E, A, carotenoids and vegetable conutrients.

Hypolipidemic effects of synthetic guggulsterones in normal rats and assessment of its long-term toxicity at cellular levels in various organs.

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Indian J Med Sci (India) Mar 1996, 50 (3) p63-7

Synthetic guggulsterones when administered to rats for a period of 3 weeks in dose of 5.0 mg/kg body weight/day caused a reduction in levels of total cholesterol by 30%, LDL-chol. by 40%, Tg by 40%. VLDL-chol. by 40% and HDL-chol. by 35%. The drug when administered to rats for a period of 16 weeks with increasing dose upto 1150 mg/kg body weight/day, reduced VLDL-chol. and Tg. by 55% and 50% respectively (P < 0.001) and LDL-chol by 33% (P < 0.05), whereas HDL-chol. was increased by 25% (P < 0.001). Histopathological studies on liver, spleen, intestine, lung, kidney, stomach and adrenal gland revealed drug related changes in a few animals upon exposure to high dose of the drug.

Effects of S-allyl cysteine sulfoxide isolated from *Allium sativum* Linn and gugulipid on some enzymes and fecal excretions of bile acids and sterols in cholesterol fed rats.

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Department of Bio-Chemistry, University of Kerala, Thiruvananthapuram, India.
Indian J Exp Biol (India) Oct 1995, 33 (10) p749-51

S-allyl cysteine sulfoxide, isolated from garlic, *A. sativum*, is more or less as active as gugulipid in controlling hypercholestermia, obesity and derangement of enzyme activities in cholesterol diet fed rats. The beneficial effects of the drugs are partly due to their inhibitory effects on transaminases, alkaline phosphatase, lipogenic enzymes and HMG CoA reductase and partly due to their stimulatory effects on plasma lecithin- cholesterol acyl transferase lipolytic enzymes and fecal excretion of sterols and bile acids.

Antiperoxide effects of S-allyl cysteine sulphoxide isolated from *Allium sativum* Linn and gugulipid in cholesterol diet fed rats.

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Department of Biochemistry, University of Kerala, India.
Indian J Exp Biol (India) May 1995, 33 (5) p337-41

Cholesterol containing diet significantly increased not only the body weight, but also the weight of liver and adipose tissue of rats. This is accompanied by a significant increase in blood lipids, atherogenic index and lipid peroxidation and a significant decrease in reduced glutathione level, superoxide dismutase and catalase activities in tissues. Treatment with S-allyl cysteine sulphoxide reverses the deleterious effects of cholesterol diet significantly and almost as effectively as gugulipid.

Clinical trials with gugulipid. A new hypolipidaemic agent

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J Assoc Physicians India (India) May 1989, 37 (5) p323-8

Multicentric clinical trials of the efficacy of gugulipid conducted at Bombay, Bangalore, Delhi, Jaipur, Lucknow, Nagpur and Varanasi have been reported. Two hundred and five patients completed 12 week open trial with gugulipid in a dose of 500 mg tds after 8 week diet and placebo therapy. One patient showed gastrointestinal symptoms which did not necessitate withdrawal of the drug. A significant lowering of serum cholesterol (av. 23.6%) and serum triglycerides (av. 22.6%) was observed in 70-80% patients Double-blind, crossover study was

completed in 125 patients with gugulipid therapy and in 108 patients with clofibrate therapy. Two patients had flu-like syndrome with clofibrate and opted out from the study. With gugulipid the average fall in serum cholesterol and triglycerides was 11 and 16.8% respectively and with clofibrate 10 and 21.6% respectively. The lipid lowering effect of both drugs became evident 3-4 week after starting the drug and had no relationship with age, sex, and concomitant drug intake. Hypercholesterolaemic patients responded better to gugulipid therapy than hypertriglyceridaemic patients who responded better to clofibrate therapy. In mixed hyperlipidaemic patients response to both drugs was comparable. HDL-cholesterol was increased in 60% cases who responded to gugulipid therapy. Clofibrate had no effect on HDL-cholesterol. A significant decrease in LDL-cholesterol was observed in the responder group to both drugs.

Nicotinic acid treatment shifts the fibrinolytic balance favourably and decreases plasma fibrinogen in hypertriglyceridaemic men

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J Cardiovasc Risk, 1997 Jun, 4:3, 165-71

BACKGROUND: Nicotinic acid in gram doses decreases cholesterol and triglyceride concentrations in plasma, but the effect on haemostatic function is not known.

METHODS: Twenty-three men with hypertriglyceridaemia were treated with 4 g nicotinic acid daily for 6 weeks. Tests for haemostatic function and serum lipoproteins were performed before and at the end of the period of treatment.

RESULTS: Treatment with nicotinic acid had the expected effect on lipoprotein concentrations: it reduced the serum concentrations of triglyceride and the three major density fractions of triglyceride (very low density lipoprotein (VLDL), low density lipoprotein (LDL) and high density lipoprotein (HDL)). The VLDL cholesterol concentration was reduced, but that of HDL cholesterol was increased (all $P < 0.0001$). The lipoprotein(a) (Lp(a)) concentration decreased significantly ($P < 0.01$). The total fibrinolytic activity was increased by nicotinic acid treatment as indicated by decreases in plasminogen activator inhibitor-1 activity from 34.3 to 23.8 U/ml ($P < 0.01$) and in alpha2-antiplasmin activity from 1.10 to 0.97 U/ml ($P < 0.01$). The plasma fibrinogen concentration decreased from 3.55 to 3.01 U/ml ($P < 0.01$). Multivariate analysis showed that the changes in alpha2-antiplasmin and Lp(a) concentrations could explain 53% of the change in plasma fibrinogen, suggesting that increased plasmin mobilization could be responsible for the decrease in plasma fibrinogen.

CONCLUSION: This study of hypertriglyceridaemic men has shown that long-term treatment with nicotinic acid not only corrects serum lipoprotein

abnormalities, but also reduces the fibrinogen concentration in plasma and stimulates fibrinolysis.

Clinical trial experience with extended-release niacin (Niaspan): dose-escalation study.

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Am J Cardiol, 1998 Dec 17, 82:12A, 35U-38U; discussion 39U-41U

Niacin is a useful lipid-modifying drug because it (1) decreases low-density lipoprotein (LDL) cholesterol, total cholesterol, triglycerides, and lipoprotein(a), and (2) raises high-density lipoprotein (HDL) cholesterol. Its use tends to be limited by side effects and inconvenient dosing regimens. The availability of an extended-release preparation (Niaspan-which has safety and efficacy similar to immediate-release niacin but which can be given once a day) provides an opportunity to increase the use of this effective lipid-modifying agent. To study the safety and efficacy of escalating doses of extended-release niacin, hyperlipidemic patients were randomly assigned to placebo or Niaspan. A forced dose-titration was done with the dosage increasing by 500 mg every 4 weeks to a maximum of 3,000 mg/day. Niaspan showed dose-related changes in total, LDL, and HDL cholesterol levels, triglycerides, cholesterol/HDL ratio, and lipoprotein(a). At a dosage of 2,000 mg/day, total cholesterol decreased by 12.1%, LDL cholesterol by 16.7%, triglycerides by 34.5%, and lipoprotein(a) by 23.6%; HDL cholesterol increased by 25.8%. Flushing was the most commonly reported side effect; flushing episodes tended to decrease with time despite an increasing dose of niacin. Of the reported side effects, only pruritus and rash were significantly different between the 2 groups. Aspartate aminotransferase, lactate dehydrogenase, and uric acid increased in a dose-dependent fashion, but fasting blood sugar increased by about 5% across most dosages. Two subjects had aspartate aminotransferase levels greater than twice the upper limit of normal, but there were no subjects in whom transaminases increased to 3 times the upper limit of normal. Women tended to have a greater LDL cholesterol response to the medication and also experienced more side effects, especially at higher dosages. Thus, the use of lower dosages of niacin may be desirable in women. The results of this dose-escalation study show beneficial effects of Niaspan on the entire lipid profile. At the maximum recommended dosage of 2,000 mg/day, all lipid and lipoprotein levels changed in desirable directions. Side effects (other than flushing) and blood chemistries were comparable to those seen with immediate-release niacin.

Hypolipidemic action of curcumin, the active principle of turmeric (*Curcuma longa*) in streptozotocin induced diabetic rats

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Molecular and Cellular Biochemistry (Netherlands), 1997, 166/1-2 (169-175)

Streptozotocin-induced diabetic rats were maintained on 0.5% curcumin containing diet for 8 weeks. Blood cholesterol was lowered significantly by dietary curcumin in these diabetic animals. Cholesterol decrease was exclusively from LDL-VLDL fraction. Significant decrease in blood triglyceride and phospholipids was also brought about by dietary curcumin in diabetic rats. In a parallel study, wherein diabetic animals were maintained on a high cholesterol diet, the extents of hypercholesterolemia and phospholipidemia were still higher compared to those maintained on control diet. Curcumin exhibited lowering of cholesterol and phospholipid in these animals also. Liver cholesterol, triglyceride and phospholipid contents were emin showed a distinct tendency to counter these changes in lipid fractions of liver. This effect of curcumin was also seen in diabetic animals maintained on high cholesterol diet. Dietary curcumin also showed significant countering of renal cholesterol and triglycerides elevated in diabetic rats. In order to understand the mechanism of hypocholesterolemic action of dietary curcumin, activities of hepatic cholesterol-7 α -hydroxylase and HMG CoA reductase were measured. Hepatic cholesterol-7 α -hydroxylase activity was markedly higher in curcumin fed diabetic animals suggesting a higher rate of cholesterol catabolism.

Effects of S-allyl cysteine sulfoxide isolated from *Allium sativum* Linn and gugulipid on some enzymes and fecal excretions of bile acids and sterols in cholesterol fed rats

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Indian Journal of Experimental Biology (India), 1995, 33/10 (749-751)

S-allyl cysteine sulfoxide, isolated from garlic, *A. sativum*, is more or less as active as gugulipid in controlling hypercholesterolemia, obesity and derangement of enzyme activities in cholesterol diet fed rats. The beneficial effects of the drugs are partly due to their inhibitory effects on transaminases, alkaline phosphatase, lipogenic enzymes and HMG CoA reductase and partly due to their stimulatory effects on plasma lecithin-cholesterol acyl transferase lipolytic enzymes and fecal excretion of sterols and bile acids.

Antiperoxide effects of S-allyl cysteine sulphoxide isolated from *Allium sativum* Linn and gugulipid in cholesterol diet fed rats

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Indian Journal of Experimental Biology (India), 1995, 33/5 (337-341)

Cholesterol containing diet significantly increased not only the body weight, but also the weight of liver and adipose tissue of rats. This is accompanied by a significant increase in blood lipids, atherogenic index and lipid peroxidation and a significant decrease in reduced glutathione level, superoxide dismutase and catalase activities in tissues. Treatment with S-allyl cysteine sulphoxide reverses the deleterious effects of cholesterol diet significantly and almost as effectively as gugulipid.

Cholesterol biosynthesis inhibitory component from *Zingiber officinale* Roscoe

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Chem Pharm Bull (Tokyo) (Japan) Apr 1993, 41 (4) p710-3

We previously reported on the isolation and identification of (E)-8 beta,17-epoxylabd-12-ene-15,16-dial (ZT) from ginger (rhizome of *Zingiber officinale* Roscoe, Zingiberaceae). In this paper, the pharmacological effects of ZT are reported. The experimental mouse hypercholesterolemia induced by Triton WR-1339 was treated after oral administration of ZT. In homogenated rat liver with ZT, cholesterol biosynthesis was decreased. In addition, the same activity was observed in the homogenated rat liver which was resected after the oral administration of ZT. According to the results of general pharmacological screening, no remarkable activity of ZT was observed except for an inhibitory effect on the cholesterol biosynthesis.

Effect of psyllium in hypercholesterolemia at two monounsaturated fatty acid intakes.

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We performed two studies to determine whether the lipid-lowering effect of viscous soluble fiber was modified by monounsaturated fatty acid (MUFA). First, psyllium (1.4 g/MJ) was compared with wheat bran (control) in 1-mo metabolic diets by using a randomized crossover design (n = 32 hyperlipidemic subjects). The background diet contained approximately 6% of energy as MUFA (20% of total fat). The second study (n = 27 hyperlipidemic subjects) was similar to the first but the background diet contained approximately 12% MUFA (29% of total fat) because of the addition of canola oil. At both fat intakes, psyllium resulted in

significant reductions in total, low-density-lipoprotein (LDL), and high-density-lipoprotein (HDL) cholesterol compared with the wheat bran control. For the psyllium diet at 6% compared with 12% MUFA, the decreases in LDL cholesterol were 12.3 +/- 1.5% (P < 0.001) and 15.3 +/- 2.4% (P < 0.001), respectively. With the higher-MUFA diet triacylglycerol fell significantly over the control phase (16.6 +/- 5.5%, P = 0.006) and the ratio of LDL to HDL cholesterol fell significantly over the psyllium phase (7.3 +/- 2.8%, P = 0.015). Psyllium and MUFA intakes were negatively related to the percentage change in the ratio of LDL to HDL cholesterol (r = -0.34, P = 0.019 and r = -0.44, P = 0.002, respectively). Chenodeoxycholate synthesis rate increased (30 +/- 13%, P = 0.038) with the psyllium diet in the 12 subjects in whom this was assessed. We conclude that psyllium lowered LDL- and HDL-cholesterol concentrations similarly at both MUFA intakes. However, there may be some advantage in combining soluble fiber and MUFA to reduce the ratio of LDL to HDL cholesterol.

Wheat bread supplemented with depolymerized guar gum reduces the plasma cholesterol concentration in hypercholesterolemic human subjects.

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Am J Clin Nutr (United States) Jan 1997, 65 (1) p107-13

Recent human studies have shown that the physiologic effects of guar gum are not diminished by partial depolymerization of its galactomannan fraction. We evaluated the effect of depolymerized guar galactomannan on fasting plasma cholesterol and triacylglycerol concentrations in healthy volunteers with moderately raised plasma cholesterol concentrations (range: 5.2-8.0 mmol/L). This study was designed as a randomized, double-blind crossover of two 3-wk feeding periods separated by a 4-wk washout period. Control and guar wheat breads were prepared by a commercial bread-making process. Subjects (n = 11) were asked to replace their normal bread with that provided, receiving control bread for one 3-wk period and guar bread for the other period, without altering their baseline diet. Subjects recorded their intake of foods for 6 consecutive days on three occasions during the study. Fasting venous blood samples (10 mL) were taken from subjects on two consecutive mornings at the start and end of each feeding period. No significant changes in body weight or dietary intake were recorded in the control and guar bread periods. There was a significant reduction (10%) in total plasma cholesterol concentration after the guar treatment (P < 0.001), mainly because of a reduction in the low-density-lipoprotein-cholesterol fraction. No changes in plasma high-density-lipoprotein-cholesterol or triacylglycerol concentrations were seen. The cholesterol-lowering effect of partially depolymerized guar gum appears to be of a magnitude similar to that of high-molecular-weight guar gum used in earlier studies.

Eicosapentaenoic acid, but not docosahexaenoic acid, increases mitochondrial fatty acid oxidation and upregulates 2,4-dienoyl-CoA reductase gene expression in rats.

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Lipids (United States) Jun 1996, 31 (6) p579-92

The aim of the present study was to investigate whether eicosapentaenoic acid (EPA) or docosahexaenoic acid (DHA) was responsible for the triglyceride-lowering effect of fish oil. In rats fed a single dose of EPA as ethyl ester (EPA-EE), the plasma concentration of triglycerides was decreased at 8 h after acute administration. This was accompanied by an increased hepatic fatty acid oxidation and mitochondrial 2,4-dienoyl-CoA reductase activity. The steady-state level of 2,4-dienoyl-CoA reductase mRNA increased in parallel with the enzyme activity. An increased hepatic long-chain acyl-CoA content, but a reduced amount of hepatic malonyl-CoA, was obtained at 8 h after acute EPA-EE treatment. On EPA-EE supplementation, both EPA (20:5n-3) and docosapentaenoic acid (DPA, 22:5n-3) increased in the liver, whereas the hepatic DHA (22:6n-3) concentration was unchanged. On DHA-EE supplementation retroconversion to EPA occurred. No statistically significant differences were found, however, for mitochondrial enzyme activities, malonyl-CoA, long-chain acyl-CoA, plasma lipid levels, and the amount of cellular fatty acids between DHA-EE treated rats and their controls at any time point studied. In cultured rat hepatocytes, the oxidation of [1-¹⁴C]palmitic acid was reduced by DHA, whereas it was stimulated by EPA. In the in vivo studies, the activities of phosphatidate phosphohydrolase and acetyl-CoA carboxylase were unaffected after acute EPA-EE and DHA-EE administration, but the fatty acyl-CoA oxidase, the rate-limiting enzyme in peroxisomal fatty acid oxidation, was increased after feeding these n-3 fatty acids. The hypocholesterolemic properties of EPA-EE may be due to decreased 3-hydroxy-3-methylglutaryl-CoA reductase activity. Furthermore, replacement of the ordinary fatty acids, i.e., the monoenes (16:1n-7, 18:1n-7, and 18:1n-9) with EPA and some conversion to DPA concomitant with increased fatty acid oxidation is probably the mechanism leading to changed fatty acid composition. In contrast, DHA does not stimulate fatty acid oxidation and, consequently, no such displacement mechanism operates. In conclusion, we have obtained evidence that EPA, and not DHA, is the fatty acid primarily responsible for the triglyceride-lowering effect of fish oil in rats.

Soy protein concentrate and isolated soy protein similarly lower blood serum cholesterol but differently affect thyroid hormones in hamsters.

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J Nutr (United States) Aug 1996, 126 (8) p2007-11

There is a wide variation in the hypocholesterolemic response to ingestion of soy protein in humans. One possible explanation is that the different soy protein preparations used contain different spectra of biologically active components. This could affect a number of indices including thyroid hormone status. An increased level of thyroxine has been proposed as an underlying mechanism of the hypocholesterolemic effect of soy protein. The objective of this study was to determine if serum cholesterol and thyroid hormone concentrations differed because of feeding soy protein from different sources. Twenty-nine male weanling golden Syrian hamsters were fed rations containing 25 g/100 g protein from either isolated soy protein (ISP), soy protein concentrate (SPC) or casein for 35 d. Serum total cholesterol concentrations were lower in hamsters fed ISP and SPC compared with those fed casein ($P < 0.05$). No differences in cholesterol concentrations were observed in lipoprotein fractions. Serum thyroxine and free thyroxine were greater only in hamsters fed ISP than in those fed casein ($P < 0.05$), whereas triiodothyronine concentrations were higher in casein-fed than in SPC-fed hamsters ($P < 0.05$). Results indicate that protein from ISP and SPC are both effective in lowering blood cholesterol concentrations, whereas only ISP increases thyroxine concentrations. Therefore, it appears unlikely that modulation of thyroid hormone status is responsible for the cholesterol-lowering effect of soy protein.

Ascorbate administration to normal and cholesterol-fed rats inhibits in vitro TBARS formation in serum and liver homogenates.

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Life Sci (England) 1996, 58 (14) p1101-8

We have recently shown that ascorbate has a hypocholesterolemic and hypotriglyceridemic effect on rats fed a diet enriched with 1.5% cholesterol and 25% hydrogenated coconut oil (Nath diet). In this study we evaluated the effect of intraperitoneal ascorbate administration on susceptibility to lipoperoxidation either in rats fed standard or Nath diet. In normal rats ascorbate treatment decreased ($p < 0.05$) the susceptibility to lipoperoxidation induced by incubation of serum for 24 hours with 2.2 mM Cu^{++} , without altering the normal serum fatty acid profile. In rats fed Nath diet we observed a reduced susceptibility of serum to Cu^{++} -induced lipoperoxidation (36%), according with their low levels of serum unsaturated fatty acids (40% less than rats fed standard diet). In these animals ascorbate administration affects serum fatty acid profile leading to a decrease of S/U ratio from 1.6 to 1.2 without significantly modifying the susceptibility of serum to lipoperoxidation. Moreover, the production of spontaneous lipid peroxides in liver homogenates, measured as TBARS levels, was strongly inhibited by ascorbate ($p < 0.01$) in rats fed either standard or Nath diet. These data indicate that ascorbate administration exerts an antioxidant effect and that in hypercholesterolemic rats, in addition to a lipid lowering effect, ascorbate exerts a protective role against the peroxidative damage of lipids.

Cholesterol-lowering effect of soyabean lecithin in normolipidaemic rats by stimulation of biliary lipid secretion.

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Br J Nutr (England) Mar 1996, 75 (3) p471-8

The purpose of the present study was to assess the role of the liver in the plasma-cholesterol-lowering effect of soyabean lecithin. Normolipidaemic rats were fed on lecithin-enriched or control diets with the same amount of protein. The lecithin diets contained 200 g/kg high-fat commercial semi-purified soyabean lecithin (230 g/kg total lipids as soyabean phosphatidylcholine) or 200 g/kg high-fat purified soyabean lecithin (930 g/kg total lipids as soyabean phosphatidylcholine). The control diets were a lowfat diet (40 g fat/kg) and a high-fat triacylglycerol-rich diet (200 g fat/kg). The high-fat diets were isoenergetic. The cholesterol-lowering effect of the lecithin-enriched diets was associated with significantly lower levels of plasma total- and HDL-cholesterol and significantly higher levels of bile phosphatidylcholine (PC), bile salts and cholesterol. These findings suggest that the liver plays a major role in the reduction of plasma cholesterol, the increased biliary lipid being provided by both HDL and the hepatic microsomal pools of PC and cholesterol.

Effect of a combination of gemfibrozil and niacin on lipid levels.

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J Clin Pharmacol (United States) Aug 1996, 36 (8) p696-700

To determine the effect of the combination of niacin and gemfibrozil on the lipid profile, a retrospective review was conducted of 161 patients who were prescribed a combination of gemfibrozil and niacin for 6 to 12 months at a community-based lipid clinic. Low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol, total cholesterol, triglycerides, ratio of total cholesterol to HDL, alanine aminotransferase (ALT), and weight were measured at entry to the clinic, 2 months after dietary instruction, during single-agent therapy, and during combination therapy. Mean doses of niacin and gemfibrozil were 1,229 mg/day and 1,200 mg/day, respectively. Patient weight decreased significantly after dietary instruction and after institution of combination therapy. There were no significant changes in ALT levels with either single-agent therapy or with combination therapy. The combination of niacin and gemfibrozil produced marked and significant changes in lipid levels: total cholesterol and LDL decreased by 14%, HDL increased by 24%, the ratio of total cholesterol to HDL

decreased by 30%, and triglycerides decreased by 52%. The combination of niacin and gemfibrozil in the setting of dietary instruction has a marked beneficial effect on serum lipid levels, and was most effective in patients with initial levels of HDL < 40 mg/dL, triglycerides > 250 mg/dL, and LDL > 160 mg/dL. No episodes of ALT elevation or symptomatic myositis were seen.

New developments in the use of niacin for treatment of hyperlipidemia: new considerations in the use of an old drug.

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Coron Artery Dis (United States) Apr 1996, 7 (4) p321-6

Niacin has been used for many years to treat hyperlipidemia. It has been shown to reduce coronary death and non-fatal myocardial infarction and, in a separate analysis of long-term (15-year) follow-up, all cause mortality. It reduces total cholesterol, low density lipoprotein cholesterol (LDL-C) and triglycerides and increases high density lipoprotein cholesterol (HDL-C). Sustained-release niacin may be associated with more dramatic changes in LDL-C and triglyceride, whereas the short acting preparation causes greater increases in HDL-C. The increase of HDL-C occurs at a lower dose (1500 mg/day) than the reduction of LDL-C (> 1500 mg/day). Niacin also favorably influences other lipid parameters including lipoprotein(a) [Lp(a)], alimentary lipemia, familial defective apolipoprotein B-100 and small dense LDL. Combination of niacin with a bile acid sequestrant or a reductase inhibitor represents a powerful lipid-altering regimen. Whereas the reductase inhibitors and bile acid binding resins primarily affect LDL-C, the combined therapy has a synergistic effect to reduce LDL-C and, in addition, the niacin reduces triglycerides and increases HDL-C. The major drawback in the use of niacin is associated side effects (flushing and palpitations) and toxicity (worsening of diabetes control, exacerbation of peptic ulcer disease, gout, hepatitis). Niacin has a long history of use as a lipid lowering agent and has several attractive features. Unfortunately, the side effect profile of this agent warrants its use only in patients with marked dyslipidemia in whom side effects and potential toxicity are closely monitored. (47 Refs.)

Effect of supplementary antioxidant vitamin intake on carotid arterial wall intima-media thickness in a controlled clinical trial of cholesterol lowering.

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Circulation (United States) Nov 15 1996, 94 (10) p2369-72

BACKGROUND: There is accumulating experimental, epidemiological, and clinical evidence of an association between anti-oxidant vitamin intake and

reduced risk of coronary heart disease. Using data from the Cholesterol Lowering Atherosclerosis Study (CLAS), we explored the association of self-selected supplementary antioxidant vitamin intake on the rate of progression of early preintrusive atherosclerosis.

METHODS AND RESULTS: CLAS was an arterial imaging trial in which nonsmoking 40- to 59-year-old men with previous coronary artery bypass graft surgery were randomized to colestipol/niacin plus diet or placebo plus diet. The rate of progression of early preintrusive atherosclerosis was determined in 146 subjects using high-resolution B-mode ultrasound quantification of the distal common carotid artery far wall intima-media thickness (IMT). From the nutritional supplement database, 22 subjects had an on-trial average supplementary vitamin E intake of ≥ 100 IU per day (high users) and 29 subjects had an average on-trial supplementary vitamin C intake of ≥ 250 mg per day (high users). Within the placebo group, less carotid IMT progression was found for high supplementary vitamin E users when compared with low vitamin E users (0.008 versus 0.023 mm/y, $P = .03$). No effect of vitamin E within the drug group was found. No effect of vitamin C within the drug or placebo group was found.

CONCLUSIONS: Supplementary vitamin E intake appears to be effective in reducing the progression of atherosclerosis in subjects not treated with lipid-lowering drugs while the process is still confined to the arterial wall (early preintrusive atherosclerosis).

Clinical trial of wax-matrix sustained-release niacin in a Russian population with hypercholesterolemia.

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Arch Fam Med (United States) Nov-Dec 1996, 5 (10) p567-75

OBJECTIVE: To assess the clinical effectiveness and tolerability of wax-matrix, controlled-release nicotinic acid (CNA) in persons with hypercholesterolemia.

DESIGN: Randomized, double-blind, placebo controlled, crossover trial.

SETTING: Ambulatory clinic at an academic cardiology center in Moscow, Russia.

PATIENTS: A volunteer sample of 135 men and women, aged 20 to 70 years, with hypercholesterolemia greater than 5.82 mmol/L (225 mg/dL) (70th-95th percentile for age and sex) who otherwise met study inclusion and exclusion criteria, were initially recruited into the study. Cholesterol levels were reduced to less than 5.82 mmol/L (225 mg/dL) in 46 subjects who participated in the initial diet intervention and were excluded from the drug intervention. Eighty-nine

subjects were randomized into the clinical trial; 4 subjects (4.5%) dropped out of the study because of intolerance of CNA.

INTERVENTION: Eight weeks of diet alone (American Heart Association Step I Diet) was followed by randomization to 2 treatment groups (1500 mg/d CNA [ENDURACIN] or placebo) for 2 months followed by a crossover of treatments for 2 months, followed by all subjects taking 2000 mg/d of CNA for 2 months.

MAIN OUTCOME MEASURES: Significant improvements in baseline measures for total serum cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) were observed after initial diet (TC, 6%; LDL-C, 6%; $P < .001$, t test), after 1500 mg/d CNA (TC, 14%; LDL-C, 18%; $P < .001$, t test), and after 2000 mg/d CNA (TC, 16%; LDL-C, 21%; $P < .001$, t test). Triglyceride, high-density lipoprotein cholesterol, and lipoprotein(a) levels also improved. No serious toxic reactions were encountered, and 4 subjects withdrew from the study because of intolerance of cutaneous and gastrointestinal adverse effects.

CONCLUSION: Wax-matrix CNA is an effective and well-tolerated pharmacological treatment for hypercholesterolemia.

Combination therapy with low-dose lovastatin and niacin is as effective as higher-dose lovastatin.

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Pharmacotherapy (United States) May-Jun 1996, 16 (3) p419-23

STUDY OBJECTIVES. To determine if low-dose lovastatin in combination with niacin causes a greater percentage reduction in low-density lipoprotein (LDL) cholesterol than lovastatin alone, and to determine if the combination increases the risk of serious adverse effects. **design.** Prospective, randomized, open-label, clinical trial. **setting.** Family medicine clinic of a university-affiliated hospital. **Patients.** Patients with fasting LDL cholesterol concentrations of at least 150 mg/dl after 4 weeks of dietary stabilization and washout of any cholesterol-lowering drugs.

INTERVENTIONS. Twenty-eight patients received lovastatin 20 mg/day for 4 weeks after dietary stabilization and washout. If LDL cholesterol remained above 130 mg/dl (100 mg/dl in patients with coronary artery disease), they were randomized to receive either lovastatin 40 mg/day or a combination of lovastatin 20 mg/day and niacin 500 mg 3 times/day.

MEASUREMENTS AND MAIN RESULTS. There was no difference in actual or percentage reductions of LDL cholesterol, total cholesterol, and triglycerides between the groups. A greater increase in high-density lipoprotein (HDL) cholesterol occurred with combination therapy ($p = 0.024$). There was no

difference in liver function tests, glucose, or uric acid between the therapies. Based on drug-acquisition cost, combination therapy is approximately 40% less expensive than monotherapy.

CONCLUSION. Low-dose niacin plus low-dose lovastatin was as effective as higher-dose lovastatin in lowering total cholesterol, LDL cholesterol, and triglyceride levels. The combination may offer benefit in raising HDL cholesterol levels.

Clinical trials with gugulipid. A new hypolipidaemic agent

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J Assoc Physicians India (India) May 1989, 37 (5) p323-8

Multicentric clinical trials of the efficacy of gugulipid conducted at Bombay, Bangalore, Delhi, Jaipur, Lucknow, Nagpur and Varanasi have been reported. Two hundred and five patients completed 12 week open trial with gugulipid in a dose of 500 mg tds after 8 week diet and placebo therapy. One patient showed gastrointestinal symptoms which did not necessitate withdrawal of the drug. A significant lowering of serum cholesterol (av. 23.6%) and serum triglycerides (av. 22.6%) was observed in 70-80% patients. Double-blind, crossover study was completed in 125 patients with gugulipid therapy and in 108 patients with clofibrate therapy. Two patients had flu-like syndrome with clofibrate and opted out from the study. With gugulipid the average fall in serum cholesterol and triglycerides was 11 and 16.8% respectively and with clofibrate 10 and 21.6% respectively. The lipid lowering effect of both drugs became evident 3-4 week after starting the drug and had no relationship with age, sex, and concomitant drug intake. Hypercholesterolaemic patients responded better to gugulipid therapy than hypertriglyceridaemic patients who responded better to clofibrate therapy. In mixed hyperlipidaemic patients response to both drugs was comparable. HDL-cholesterol was increased in 60% cases who responded to gugulipid therapy. Clofibrate had no effect on HDL-cholesterol. A significant decrease in LDL-cholesterol was observed in the responder group to both drugs.

Hypolipidemic and antioxidant effects of Commiphora mukul as an adjunct to dietary therapy in patients with hypercholesterolemia

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Cardiovasc Drugs Ther (United States) Aug 1994, 8 (4) p659-64

The effects of the administration of 50 mg of guggulipid or placebo capsules twice daily for 24 weeks were compared as adjuncts to a fruit- and vegetable-enriched prudent diet in the management of 61 patients with hypercholesterolemia

(31 in the guggulipid group and 30 in the placebo group) in a randomized, double-blind fashion. Guggulipid decreased the total cholesterol level by 11.7%, the low density lipoprotein cholesterol (LDL) by 12.5%, triglycerides by 12.0%, and the total cholesterol/high density lipoprotein (HDL) cholesterol ratio by 11.1% from the postdiet levels, whereas the levels were unchanged in the placebo group. The HDL cholesterol level showed no changes in the two groups. The lipid peroxides, indicating oxidative stress, declined 33.3% in the guggulipid group without any decrease in the placebo group. The compliance of patients was greater than 96%. The combined effect of diet and guggulipid at 36 weeks was as great as the reported lipid-lowering effect of modern drugs. After a washout period of another 12 weeks, changes in blood lipoproteins were reversed in the guggulipid group without such changes in the placebo group. Side effects of guggulipid were headache, mild nausea, eructation, and hiccup in a few patients.

Beneficial effects of *Allium sativum* (garlic), *Allium cepa* and *Commiphora mukul* on experimental hyperlipidemia and atherosclerosis--a comparative evaluation.

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J Postgrad Med (India) Jul 1991, 37 (3) p132-5

Oral administration of petroleum ether extract of *Allium sativum*, *Allium cepa* and ethylacetate extract of *Commiphora mukul* in albino rats significantly prevented rise in serum cholesterol and serum triglyceride level, caused by atherogenic diet. All the three agents were also found to confer significant protection against atherogenic diet induced atherosclerosis.

Curcumin, a major component of food spice turmeric (*Curcuma longa*) inhibits aggregation and alters eicosanoid metabolism in human blood platelets

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Prostaglandins Leukotrienes and Essential Fatty Acids (United Kingdom), 1995, 52/4 (223-227)

In traditional medicine, Ayurveda, several spices and herbs are held to possess medicinal properties. Earlier we have reported that extracts from several spices, including turmeric, inhibit platelet aggregation and modulate eicosanoid biosynthesis. Due to their eicosanoid-modulating property, it was suggested that the spices may serve to provide clues to drugs directed to arachidonic acid (AA) pathway enzymes as pharmacological targets. Curcumin, a major component of turmeric, inhibited platelet aggregation induced by arachidonate, adrenaline and

collagen. This compound inhibited thromboxane B2 (TXB2) production from exogenous (14C) arachidonate in washed platelets with a concomitant increase in the formation of 12-lipoxygenase products. Moreover, curcumin inhibited the incorporation of (14C)AA into platelet phospholipids and inhibited the deacylation of AA-labelled phospholipids (liberation of free AA) on stimulation with calcium ionophore A23187. Curcumin's anti-inflammatory property may, in part, be explained by its effects on eicosanoid biosynthesis.

Influence of capsaicin, eugenol, curcumin and ferulic acid on sucrose-induced hypertriglyceridemia in rats

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Nutr. Rep. Int. (USA), 1988, 38/3 (571-581)

The spice active principles, capsaicin, eugenol curcumin and 'ferulic acid' a common plant constituent were found to counter many of the metabolic changes caused by a high sucrose diet fed to rats. The compounds tested at high and low levels were mostly found to lower or tend to lower liver weight, liver triglycerides, free fatty acids, phospholipids, serum total, VLDL+LDL and HDL triglycerides, VLDL+LDL cholesterol, free fatty acids and also elevate serum total and HDL cholesterol.

Inhibitory effect of curcumin, an anti-inflammatory agent, on vascular smooth muscle cell proliferation

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Eur. J. Pharmacol. (Netherlands), 1992, 221/2-3 (381-384)

The effects of curcumin, an anti-inflammatory agent from *Curcuma longa*, on the proliferation of blood mononuclear cells and vascular smooth muscle cells were studied. Proliferative responses were determined from the uptake of tritiated thymidine. In human peripheral blood mononuclear cells, curcumin dose dependently inhibited the responses to phytohemagglutinin and mixed lymphocyte reaction at the dose ranges of 10^{-6} to 3×10^{-5} and 3×10^{-6} to 3×10^{-5} M, respectively. Curcumin (10^{-6} to 10^{-4} M) dose dependently inhibited the proliferation of rabbit vascular smooth muscle cells stimulated by fetal calf serum. Curcumin had a greater inhibitory effect on platelet-derived growth factor-stimulated proliferation than on serum-stimulated proliferation. Cinnamic acid, coumaric acid and ferulic acid were much less effective than curcumin as inhibitors of serum-induced smooth muscle cell proliferation, suggesting that the cinnamic acid and ferulic acid moieties alone are not sufficient for activity, and

that the characteristics of the diferuloylmethane molecule itself are necessary for activity. Curcumin may be useful as a new template for the development of better remedies for the prevention of the pathological changes of atherosclerosis and restenosis.

Polyphenols as cancer chemopreventive agents.

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J Cell Biochem Suppl (United States) 1995, 22 p169-80

This article summarizes available data on the chemopreventive efficacies of tea polyphenols, curcumin and ellagic acid in various model systems. Emphasis is placed upon the anticarcinogenic activity of these polyphenols and their proposed mechanism(s) of action. Tea is grown in about 30 countries and, next to water, is the most widely consumed beverage in the world. Tea is manufactured as either green, black, or oolong; black tea represents approximately 80% of tea products. Epidemiological studies, though inconclusive, suggest a protective effect of tea consumption on human cancer. Experimental studies of the antimutagenic and anticarcinogenic effects of tea have been conducted principally with green tea polyphenols (GTPs). GTPs exhibit antimutagenic activity in vitro, and they inhibit carcinogen-induced skin, lung, forestomach, esophagus, duodenum and colon tumors in rodents. In addition, GTPs inhibit TPA-induced skin tumor promotion in mice. Although several GTPs possess anticarcinogenic activity, the most active is (-)-epigallocatechin-3-gallate (EGCG), the major constituent in the GTP fraction. Several mechanisms appear to be responsible for the tumor-inhibitory properties of GTPs, including enhancement of antioxidant (glutathione peroxidase, catalase and quinone reductase) and phase II (glutathione-S-transferase) enzyme activities; inhibition of chemically induced lipid peroxidation; inhibition of irradiation- and TPA-induced epidermal ornithine decarboxylase (ODC) and cyclooxygenase activities; inhibition of protein kinase C and cellular proliferation; antiinflammatory activity; and enhancement of gap junction intercellular communication. Curcumin is the yellow coloring agent in the spice tumeric. It exhibits antimutagenic activity in the Ames Salmonella test and has anticarcinogenic activity, inhibiting chemically induced preneoplastic lesions in the breast and colon and neoplastic lesions in the skin, forestomach, duodenum and colon of rodents. In addition, curcumin inhibits TPA-induced skin tumor promotion in mice. The mechanisms for the anticarcinogenic effects of curcumin are similar to those of the GTPs. Curcumin enhances glutathione content and glutathione-S-transferase activity in liver; and it inhibits lipid peroxidation and arachidonic acid metabolism in mouse skin, protein kinase C activity in TPA-treated NIH 3T3 cells, chemically induced ODC and tyrosine protein kinase activities in rat colon, and 8-hydroxyguanosine formation in mouse fibroblasts. Ellagic acid is a polyphenol found abundantly in various fruits, nuts and vegetables. Ellagic acid is active in antimutagenesis assays, and has been

shown to inhibit chemically induced cancer in the lung, liver, skin and esophagus of rodents, and TPA-induced tumor promotion in mouse skin.

Anti-tumour and antioxidant activity of natural curcuminoids.

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Cancer Lett (Ireland) Jul 20 1995, 94 (1) p79-83

Matural curcuminoids, curcumin, I, II and III isolated from turmeric (*Curcuma longa*) were compared for their cytotoxic, tumour reducing and antioxidant activities. Curcumin III was found to be more active than the other two as a cytotoxic agent and in the inhibition of Ehrlich ascites tumour in mice (ILS 74.1%). These compounds were also checked for their antioxidant activity which possibly indicates their potential use as anti-promoters. The amount of curcuminoids (I, II and III) needed for 50% inhibition of lipid peroxidation was 20, 14 and 11 g/m. Concentrations needed for 50% inhibition of superoxides were 6.25, 4.25 and 1.9 micrograms/ml and those for hydroxyl radical were 2.3, 1.8 and 1.8 micrograms/ml, respectively. The ability of these compounds to suppress the superoxide production by macrophages activated with phorbol-12-myristate-13-acetate (PMA) indicated that all the three curcuminoids inhibited superoxide production and curcumin III produced maximum effect. These results indicate that curcumin III is the most active of the curcuminoids present in turmeric. Synthetic curcumin I and III had similar activity to natural curcumins.

Phospholipid epitopes for mouse antibodies against bromelain-treated mouse erythrocytes.

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Immunology (England) Sep 1987, 62 (1) p11-6

The reactivity of mouse antibodies against bromelain-treated mouse erythrocytes (BrMRBC) with phospholipid epitopes was assessed by ELISA, using four clones of monoclonal anti-BrMRBC antibodies that had idiotypes distinct from one another. The four antibodies could bind to low-density lipoproteins (LDL) from human and chicken, but not to LDL from mouse and rat. As to liposomes of natural phospholipids, all the clones reacted with liposomes of phosphatidylcholine, and some of them could react with liposomes of sphingomyelin, phosphatidylglycerol, phosphatidyl acid or cardiolipin. For liposomes of synthetic phosphatidylcholine with different fatty acids, the length of carbon chains and the number of unsaturated carbon chains of the fatty acids markedly affected the binding of each monoclonal antibody to the liposomes. The addition of dicetyl phosphate or stearylamine to phosphatidylcholine liposomes

changed the reactivity of the liposomes. These results support the view that mouse anti-BrMRBC antibodies can recognize appropriately spaced phosphorylcholine residues on the surface of phospholipid liposomes, LDL and cells. The four clones had similar capacities for binding to LDL as well as to BrMRBC, but they had obviously different capacities for binding to phospholipid liposomes; the epitopes on phospholipid liposomes used in the present study were not so perfect as to react well with every anti-BrMRBC antibody.

The effect of spices on cholesterol 7 alpha-hydroxylase activity and on serum and hepatic cholesterol levels in the rat.

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Int J Vitam Nutr Res (Switzerland) 1991, 61 (4) p364-9

The effect of feeding curcumin, capsaicin, ginger, mustard, black pepper and cumin on cholesterol and bile acid metabolism was studied in rats. The activity of hepatic cholesterol-7 alpha-hydroxylase, the rate-limiting enzyme of bile acid biosynthesis, was significantly elevated in curcumin (turmeric), capsaicin (red pepper), ginger and mustard treated animals. The enzyme activity was comparable to controls in black pepper and cumin fed rats. Serum and liver microsomal cholesterol contents were significantly higher in the curcumin and capsaicin treated animals. Thus, this study has suggested that the spices--turmeric, red pepper, ginger and mustard can stimulate the conversion of cholesterol to bile acids, an important pathway of elimination of cholesterol from the body. However, simultaneous stimulation of cholesterol synthesis by the spice principles--curcumin and capsaicin suggests that there may not be any significant contribution of stimulation of bile acid biosynthesis to the hypocholesterolemic action of these spices, and the latter action may solely be due to interference with exogenous cholesterol absorption.

Effect of gugulipid on bioavailability of diltiazem and propranolol.

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J Assoc Physicians India (India) Jun 1994, 42 (6) p454-5

The effect of single oral dose of 1 gm gugulipid was studied on bioavailability of single oral dose of propranolol (40 mg) and diltiazem (60 mg) in 10 and 7 normal healthy male volunteers respectively. It was a randomised within group crossover study. Blood samples were collected at hourly intervals upto 8 hrs. Gugulipid significantly reduced ($P < .01$) peak plasma concentration (C_{max}) and area under curve (AUC 0-8 hrs) of both the drugs in normal volunteers. Such interaction in

patients receiving propranolol or diltiazem with gugulipid may lead to diminished efficacy or nonresponsiveness due to significant reduction in bioavailability.

Biological effects of isoflavones in young women: Importance of the chemical composition of soyabean products

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British Journal of Nutrition (United Kingdom), 1995, 74/4 (587-601)

To examine the hormonal effects of isoflavones, of which soyabean is a rich source, fifteen healthy non-vegetarian premenopausal women were studied over 9 months. They lived in a metabolic suite for between 4 and 6 months where their diet and activity levels were kept constant and their hormonal status was measured over two or three menstrual cycles. During one (control) menstrual cycle a normal but constant diet containing no soyabean products was fed. Then, over a second complete cycle six subjects consumed a similar diet into which 60 g textured vegetable protein (TVP)/d, containing 45 mg conjugated isoflavones, had been incorporated. Three participants had 50 g miso (a fermented soyabean paste), containing 25 mg unconjugated isoflavones, added daily to their diet over a menstrual cycle, and six others consumed 28 g TVP/d, containing 23 mg conjugated isoflavones. Five participants completed a third diet period where they were randomly assigned to consume either the control diet over a cycle, or a similar diet incorporating 60 g of a soyabean product which had had the isoflavones chemically extracted (Arcon F). Follicular phase length was significantly ($P < 0.01$) increased and peak progesterone concentrations were delayed with 60 g TVP but no effects were observed with Arcon F. The increase in menstrual cycle length did not reach statistical significance in the three subjects who ate 50 g miso/d, but peak progesterone levels were significantly ($P < 0.05$) delayed. Mid-cycle peaks of luteinizing hormone (LH) and follicle stimulating hormone (FSH) were suppressed with 45 mg conjugated isoflavones as 60 g TVP ($P < 0.05$ and $P < 0.01$ respectively). No other changes in sex-steroid hormone levels were observed on any of the other diets. A significant reduction in total cholesterol was found with 45 mg conjugated isoflavones ($P < 0.05$), but not with 23 mg conjugated isoflavone-free Arcon F. There was no effect of menstrual cycle phase on transit time.

Overview of proposed mechanisms for the hypocholesterolemic effect of soy

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Journal of Nutrition (USA), 1995, 125/3 Suppl. (606S-611S)

A large body of literature indicates that protein from soybeans reduces blood cholesterol concentrations in experimental animals as well as in humans. The mechanism and component of soy responsible has not been established fully. Some suggest that when soy protein is fed, cholesterol absorption and/or bile acid reabsorption is impaired. This is observed in some animal species, such as rabbits and rats, but not in humans nor when amino acids replace intact soy protein. Others propose that changes in endocrine status, such as alteration in insulin:glucagon ratio and thyroid hormone concentrations, are responsible. The metabolic changes that have been observed on soy protein feeding in a variety of animal models, and in some cases humans, include increased cholesterol synthesis, increased bile acid synthesis (or fecal bile acid excretion), increased apolipoprotein B or E receptor activity and decreased hepatic lipoprotein secretion and cholesterol content, which are associated with an increased clearance of cholesterol from the blood. One hypothesis suggests amino acid composition or proportionality of soy causes changes in cholesterol metabolism (possibly via the endocrine system). Others have proposed that nonprotein components (such as saponins, fiber, phytic acid, minerals and the isoflavones) associated with soy protein affect cholesterol metabolism either directly or indirectly.

Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women

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Am. J. Clin. Nutr. (USA), 1994, 60/3 (333-340)

The influence of a diet containing soy protein on the hormonal status and regulation of the menstrual cycle was examined in six premenopausal women with regular ovulatory cycles. Soy protein (60 g containing 45 mg isoflavones) given daily for 1 mo significantly ($P < 0.01$) increased follicular phase length and/or delayed menstruation. Midcycle surges of luteinizing hormone and follicle-stimulating hormone were significantly suppressed during dietary intervention with soy protein. Plasma estradiol concentrations increased in the follicular phase and cholesterol concentrations decreased 9.6%. Similar responses occur with tamoxifen, an antiestrogen undergoing clinical trial as a prophylactic agent in women at high risk for breast cancer. These effects are presumed to be due to nonsteroidal estrogens of the isoflavone class, which behave as partial estrogen agonists/antagonists. The responses to soy protein are potentially beneficial with respect to risk factors for breast cancer and may in part explain the low incidence of breast cancer and its correlation with a high soy intake in Japanese and Chinese women.

A review of the clinical effects of phytoestrogens

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Obstetrics and Gynecology (USA), 1996, 87/5 II Suppl. (897-904)

Objective: To review the sources, metabolism, potencies, and clinical effects of phytoestrogens on humans.

Data Sources: The MEDLINE data base for the years 1980-1995 and reference lists of published articles were searched for relevant English-language articles concerning phytoestrogens, soy products, and diets with high-phytoestrogen content.

Methods of Study Selection: We identified 861 articles as being relevant. Human cell line studies, human epidemiologic studies (case-control or cohort), randomized trials, and review articles were included. Animal studies regarding phytoestrogens were included when no human data were available concerning an important clinical area.

Tabulation, Integration, and Results: Included were studies containing information considered pertinent to clinical practice in the areas of growth and development, menopause, cancer, and cardiovascular disease. When findings varied, those presented in this study reflect consensus. All studies concurred that phytoestrogens are biologically active in humans or animals. These compounds inhibit the growth of different cancer cell lines in cell culture and animal models. Human epidemiologic evidence supports the hypothesis that phytoestrogens inhibit cancer formation and growth in humans. Foods containing phytoestrogens reduce cholesterol levels in humans, and cell line, animal, and human data show benefit in treating osteoporosis.

Conclusion: This review suggests that phytoestrogens are among the dietary factors affording protection against cancer and heart disease in vegetarians. With this epidemiologic and cell line evidence, intervention studies are now an appropriate consideration to assess the clinical effects of phytoestrogens because of the potentially important health benefits associated with the consumption of foods containing these compounds.

Nutritional interest of flavonoids

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Metaboliques, 63122 St-Genes-Champanelle France
Medecine et Nutrition (France), 1996, 32/1 (17-27)

Polyphenols represent a complex group of compounds including several categories such as 4-oxo-flavonoids, anthocyanins and tannins. Some of these molecules are present in substantial amounts in various beverages and in plant

foods (fruits, vegetables...), and several investigations have established that they were liable to cross the intestinal barrier in mammals. Significant concentrations of flavonoid or polyphenol metabolites are likely to circulate in blood plasma in humans, and it appears thus important to assess their potential biological effects. Some interesting properties have already been reported, especially as to 4-oxo-flavonoids: they have antioxidizing and metal-complexing properties, and they are liable to modulate the activity of enzymes governing important cell functions. By protecting L.D.L. from oxidative alterations and by affecting platelet functions and plasma cholesterol, flavonoids might play a protective role against atherosclerosis. Some 4-oxo-flavonoids (quercetin, genistein...) show antiproliferative properties in vitro and inhibit the development of chimio-induced cancers in animal models. Thus, together with other micronutriments, their occurrence in fruits and legumes could explain the preventive effects towards cancer risk of plant foods. Isoflavones which present a phytoestrogenic activity could be more specifically involved in the prevention of breast cancer risk. Further investigations are required to determine the actual bioavailability of the different classes of flavonoids, and to fully understand the underlying mechanisms of their biological effects.

Influence of dietary curcumin and cholesterol on the progression of experimentally induced diabetes in albino rat

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Molecular and Cellular Biochemistry (USA), 1995, 152/1 (13-21)

Effect of feeding 0.5% curcumin diet or 1% cholesterol diet was examined in albino rats rendered diabetic with streptozotocin injection. Diabetic rats maintained on curcumin diet for 8 weeks excreted Comparatively less amounts of albumin, urea, creatinine and inorganic phosphorus. Urinary excretion of the electrolytes sodium and potassium were also significantly lowered under curcumin treatment. Dietary curcumin also partially reversed the abnormalities in plasma albumin, urea, creatinine and inorganic phosphorus in diabetic animals. On the other hand, glucose excretion or the fasting sugar level was unaffected by dietary curcumin and so also the body weights were not improved to any significant extent. Diabetic rats fed curcumin diet had a lowered relative liver weight at the end of the study compared to other diabetic rat groups. Diabetic rats fed a curcumin diet also showed lowered lipid peroxidation in plasma and urine when compared to other diabetic groups. The extent of lipid peroxidation on the other hand, was still higher in cholesterol fed diabetic groups compared to diabetic rats fed with control diet. Thus, the study reveals that curcumin feeding improves the metabolic status in diabetic condition, despite no effect on hyperglycemic status or the body weights. The mechanism by which curcumin improves this situation is probably by virtue of its hypocholesterolemic influence, antioxidant nature and free radical scavenging property.

Effect of retinol deficiency and curcumin or turmeric feeding on brain Na⁺-K⁺ adenosine triphosphatase activity

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The effect of retinol deficiency and curcumin and turmeric feeding on brain microsomal Na⁺-K⁺ ATPase activity was investigated. The brain Na⁺-K⁺ ATPase activity registered an increase of 148.5% as compared to the control group. Upon treating retinol deficient rats with curcumin or turmeric, the abnormally elevated activity showed a decrease of 36.9 and 47.1%, respectively, when compared to the retinol deficient group. An increase in V(max) by 67% and K(m) by 66% for ATP was observed in the retinol deficient group. Curcumin or turmeric fed retinol-deficient groups reduced the V(max) by 25 and 33%, while K(m) was reduced by 25 and 31%, respectively, compared to the retinol deficient group. Arrhenius plot of Na⁺-K⁺ ATPase showed a typical bi-phasic pattern in all the groups. Cholesterol:Phospholipid ratio showed a decrease in the retinol-deficient group by 67.8%, which showed a marked increase in curcumin or turmeric treated groups. Detergents could increase the Na⁺-K⁺ ATPase activity more in the control group than in the retinol deficient groups. Curcumin or turmeric improved the detergent action on the enzyme. Subsequent freezing and thawing over a period of 30 min decreased the enzyme activity by 22.8% in the retinol deficient group compared to 15.9% decrease in the control group. Curcumin or turmeric treated groups showed a decrease in the enzyme activity by 22.0 and 19.2%, respectively, when compared to the zero time in each group. In the presence of concanavalin-A (Con-A) there was only 52.4% stimulation in the enzyme activity in retinol deficient groups, compared to 108.0% in the control group. Curcumin or turmeric treated retinol-deficient groups showed a stimulation in the presence of con-A by 70 and 99.5%, respectively.

Bioactive substances in food: Identification and potential uses

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Bioactive substances in foods can represent 'extranutritional' constituents naturally present in small quantities in the food matrix, produced upon either in vivo or industrial enzymatic digestion, the latter being a result of food-processing activities. Bioactive constituents of food evoke physiological, behavioral, and immunological effects. Evidence from both epidemiological and animal studies has suggested chemopreventative roles for phytochemicals in certain forms of

cancers and in the control of hyperlipidemia. Secondary products of plant metabolism can modulate xenobiotic metabolizing and cholesterol synthetic enzymes. Unique physicochemical properties of food-derived peptides with characteristic amino acid composition and sequences have been reported to influence intestinal transit, modify nutrient absorption and excretion, and exhibit immunostimulating and antihypertensive activity. Biologically active peptides derived from casein, fish muscle, and plant protein hydrolysates have been isolated, purified, and identified in peptide sequence studies. Therapeutic proteins (e.g., specific antibodies) derived from animal products such as milk may offer the potential for developing specialized food products with prophylactic as well as nutritive quality. This paper discusses the physicochemical mechanism of action of specific bioactive substances naturally present in or derived from foods. The biotechnologies employed to develop these products and the issues concerning acceptance by consumer and regulatory bodies are also addressed.

Mechanism of antiinflammatory actions of curcumine and boswellic acids

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Curcumine from *Curcuma longa* and the gum resin of *Boswellia serrata*, which were demonstrated to act as antiinflammatories in *in vivo* animal models, were studied in a set of *in vitro* experiments in order to elucidate the mechanism of their beneficial effects. Curcumine inhibited the 5-lipoxygenase activity in rat peritoneal neutrophils as well as the 12-lipoxygenase and the cyclooxygenase activities in human platelets. In a cell free peroxidation system curcumine exerted strong antioxidative activity. Thus, its effects on the dioxygenases are probably due to its reducing capacity. Boswellic acids were isolated from the gum resin of *Boswellia serrata* and identified as the active principles. Boswellic acids inhibited the leukotriene synthesis via 5-lipoxygenase, but did not affect the 12-lipoxygenase and the cyclooxygenase activities. Additionally, boswellic acids did not impair the peroxidation of arachidonic acid by iron and ascorbate. The data suggest that boswellic acids are specific, non-redox inhibitors of leukotriene synthesis either interacting directly with 5-lipoxygenase or blocking its translocation.

Influence of dietary spices on adrenal steroidogenesis in rats

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Experiments were carried on adult rats which were fed the following diets for 2 months: Control, Curcumin (0.5%), Capsaicin (15mg%), Ginger (50mg%), Black pepper (0.5%), Cumin (1.25%), Mustard (250mg%), Fenugreek (2%) and Onion (3%). Adrenal weights in the various experimental groups were comparable to controls. Adrenal cholesterol was found to be significantly lower in all the spice fed animals except mustard suggesting a higher rate of cholesterol turnover to corticosteroid hormones. Cholesterol depletion was accompanied by reduced ascorbic acid content in the adrenals of curcumin, capsaicin, fenugreek and onion fed rats. Urinary excretion of 17-oxo and 17-hydroxy steroids which are the metabolites of corticosteroids was significantly higher in these spice fed groups. These data are indicative of the stimulatory influence of dietary spices on adrenal steroidogenesis.

Differential effects of dietary lipids and curcumin on kidney microsomal fatty acids and Na⁺, K⁺ - ATPase activity in rat

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The effect of dietary lipids and spice principle curcumin on kidney microsomal lipids, Na⁺, K⁺ - ATPase activity and serum lipid levels were studied. Rats were fed a diet containing either coconut oil, safflower oil or menhaden oil for 8 weeks. Safflower oil and menhaden oil feeding resulted in the accumulation of n-6 polyunsaturated fatty acids (PUFA) and n-3 PUFA respectively in the kidney microsomes. The specific activity of Na⁺, K⁺ - ATPase was higher by 26% in animals fed safflower oil when compared to animals fed coconut oil or menhaden oil. Supplementation of curcumin in the diets containing different lipids did not affect either the kidney microsomal fatty acid profiles or Na⁺, K⁺ - ATPase activity. However, dietary curcumin reduced the serum triglyceride level by 44% in safflower oil fed animals and serum cholesterol levels by 24% and 31% in animals fed safflower oil and menhaden oil respectively. These studies indicated that dietary lipids and curcumin differentially affect membrane fatty acid composition, Na⁺, K⁺ - ATPase activity and serum lipids.