

## Bacterial Infections

## ABSTRACTS

- Bhimani RS., 1999. Influence of lactoferrin feeding and injection against systemic staphylococcal infections in mice.
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**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 10<sup>10</sup> 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.

Nutr Rev 1994 May;52(5):168-70

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.

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 10(8) *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  $\leq 10^5$  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, and 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 pathogens<sup>2-4</sup>. 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.**

Kuwata H, Yip TT, Tomita M, Hutchens TW. Department of Food Science and Technology, University of California, Davis 95616, USA. hidi@msn.com

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 ( $1.2 \times 10^{-4}$ ) 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  $16.9 \pm 2.7$  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.**

Marino M, Bersani C, Comi G. Department of Food Science, University of Udine, Italy. marilena.marino@dsa.uniud.it

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.

## **Intestinal health.**

Percival, M.

Clin. Nutr. Insights 1997; 5(5): 1-6.

No Abstract Available

## **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, Kashamn 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 <sup>59</sup>Fe-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%.

## **SUGGESTED READING**

### **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 E<sub>2</sub>, 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.

### **Oral administration of protease inhibits enterotoxigenic *Escherichia coli* receptor activity in piglet small intestine**

Mynott T.L.; Luke R.K.J.; Chandler D.S. Digestive Diseases Research Centre, Medical College, St Bartholomew's Hospital, Charter House Square, London EC1M 6BQ United Kingdom

Gut (United Kingdom) 1996, 38/1 (28-32)

The virulence of enterotoxigenic *Escherichia coli* (ETEC) is attributed to their ability to adhere via fimbrial adhesins to specific receptors located on the intestinal mucosa. A novel approach to preventing ETEC induced diarrhoea would be to prevent attachment of ETEC to intestine by proteolytically modifying the receptor attachment sites. This study aimed to examine the effect of bromelain, a proteolytic extract obtained from pineapple stems, on ETEC receptor activity in porcine small intestine. Bromelain was administered orally to piglets and K88sup + ETEC attachment to small intestine was measured at 50 cm intervals using an enzyme immunoassay. K88sup + ETEC attachment to intestinal sections that were not treated with bromelain varied appreciably between sampling sites. Variability in receptor activity along the intestinal surface is thought to be caused by the localised effects of endogenous proteases. Oral administration of exogenous protease inhibited K88sup + ETEC attachment to pig small intestine in a dose dependent manner (<0.05). Attachment of K88sup + ETEC was negligible after treatment, resembling the levels of attachment of K88sup + to piglets of the genetically determined non-adhesive phenotype, which are resistant to K88sup + ETEC infection. Serum biochemical analysis and histopathological examination of treated piglets showed no adverse effects of the bromelain treatment. It is concluded that administration of bromelain can inhibit ETEC receptor activity in vivo and may therefore be useful for prevention of K88sup + ETEC induced diarrhoea.

### **Mycobacteria-induced autoantibody production is associated with susceptibility to infection but not with host propensity to develop autoimmune disease**

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Clinical and Experimental Immunology (United Kingdom) 1995, 100/1 (75-80)

Mycobacteria cause increase in autoantibody production in the host during the first weeks of infection. The level of the autoantibody enhancement varies widely in different hosts, suggesting that it depends on features of the host make-up. We have investigated the participation of two characteristics of the host in the modulation of mycobacteria-induced autoantibody production: (i) the host being

genetically determined to later develop spontaneous autoimmune disease; (ii) the host being susceptible/resistant to mycobacterial infection. *Mycobacterium avium* infection was studied in 3-month-old mice that are prone (NZB and C57Bl/6-lpr/lpr strains) or not (NZW and C.D2 strains) to develop, when older, autoimmune disease; these murine strains are either naturally susceptible (C57Bl/6-lpr/lpr and NZW) or resistant (NZB and C.D2) to mycobacteria. *Mycobacterium avium* infection was produced by i.p. injection of  $3 \times 10^7$  viable bacilli. At days 15 and 30 of the infection, we determined the following parameters: (i) number of cells producing natural autoantibodies (splenic cells showing surface antibodies against bromelain-treated mouse (BrM) erythrocytes); (ii) suppression of the primary response to T cell-dependent antigen (i.e. to sheep erythrocytes); (iii) immunoglobulin classes and IgG isotypes; (iv) titres of anti-dsDNA antibodies; and (v) serum concentrations of interferon-gamma (IFN-gamma). We found that the highest elevations in natural autoantibodies were associated with hosts being naturally susceptible to mycobacteria, but not with the host being genetically determined to later develop autoimmune disease. The rise in autoantibodies was predominantly of the IgM type, being associated with suppression of the T cell response and accompanied by increase in serum IFN-gamma. Mycobacteria failed to induce any significant enhancement in pathogenic anti-dsDNA antibodies. Our data suggest that the finding of a high level of autoantibodies during the early phase of mycobacterial infection reflects host susceptibility to the infectious agent, and that it is not related with its propensity to later develop autoimmune disorders.

### **Therapy of chlamydia infections with tetracyclines**

Sanders H.J. Zweibrucker Strasse 7, D-5650 Solingen Germany

International Journal of Experimental and Clinical Chemotherapy (Germany) 1990, 3/2 (101-106)

In 7% of patients suffering from cervicitis an infection with chlamydia was detected. In a randomized study 36 patients with chlamydia infections were assigned either to a tetracycline-HCl plus bromelain (250 mg and 40 mg, respectively, four times per day) or to a doxycycline (100 mg, twice daily) treatment for a period of 14 days. After 7 days the pathogen was eliminated in 66.7% of the patients treated with tetracycline plus bromelain and in 55.6% of the patients receiving doxycycline. After the completion of the course of therapy an infection with chlamydia was no longer detectable in any patient of the two groups. The clinical effectiveness of the two therapies was considered to be good or very good in all cases. Adverse effects occurred in 11% (tetracycline + bromelain) and 16% (doxycycline) of the patients. In order to avoid complications and with respect to costs, adequate methods of identification of chlamydia infections and early antibiotic treatment, including the sexual partner, must be recommended.

### **Activation of normal murine B cells by *Echinococcus granulosus***

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Immunology (United Kingdom) 1989, 67/1 (16-20)

*Echinococcus granulosus* protoscolex (PSC) infection of BALB/c mice led, after 4 days, to raised numbers of cells forming plaques with trinitrophenyl-treated sheep red cells and bromelain-treated mouse red cells. The findings were similar in athymic and euthymic CBA mice. Activation of B cells was accompanied by secretion of immunoglobulin, as indicated by the reverse plaque technique. In addition, co-culture of PSC with the 7OZ/3 pre-B-cell line led to the induction of differentiation, resulting in the expression of surface immunoglobulin (Ig). It is concluded that *E. granulosus* is a polyclonal activator of B cells inducing both transformation and differentiation, and that the effect is thymus-independent.

### **Evidence for autoantibody production associated with polyclonal B-cell activation by *Pseudomonas aeruginosa***

Garzelli C.; Campa M.; Colizzi V.; et al. Inst. Microbiol., Univ. Pisa, 56100 Pisa Italy

Infection and Immunity (United States) 1982, 35/1 (13-19)

Experimental infection of mice with *Pseudomonas aeruginosa* resulted in the polyclonal activation of B lymphocytes, as assessed by the spontaneous plaque forming cell (PFC) response to trinitrophenyl and sheep erythrocytes. Additionally, a PFC response to bromelain-treated syngeneic erythrocytes (Br-MRBC) could be detected in infected mice, suggesting that *P. aeruginosa* infection might also induce activation of self-reactive B-cell clones and consequently lead to autoantibody production. Furthermore, in cultures of mouse peritoneal cells, heat-killed *P. aeruginosa* enhanced the development of anti-Br-MRBC PFC, even under conditions where cell division was blocked, suggesting that the in vitro *P. aeruginosa*-induced enhancement of anti-Br-MRBC PFC was essentially related to cell differentiation, cell division playing only a minor role. The mechanisms of the in vivo and in vitro *P. aeruginosa*-induced activation of anti-Br-MRBC PFC are discussed.

### **One-step synthesis of novel 2,4-diaminopyrimidine antifolates from bridged alicyclic ketones and cyanoguanidine**

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Journal of Heterocyclic Chemistry (United States) 1999, 36/3 (723-728)

A convenient one-step reaction with cyanoguanidine was used to convert alicyclic ketones to previously undescribed 2,4-diamino-5,6,7,8-tetrahydroquinazolines with a one-, two-, or three-carbon bridge in the carbocyclic ring. Although the yields of the desired products were modest, the principal advantage of this one-step process was that it provided easy access to a variety of novel bridged heterocyclic ring systems whose synthesis from sterically hindered ketones by other methods would have required multiple steps with an even lower overall yield. The products were tested as inhibitors of dihydrofolate reductases from *Pneumocystis carinii*, *Toxoplasma gondii*, and rat liver with a view to examining the effect of a space-filling bridge on binding. The most potent and selective compound in the group was 4,6-diamino-3,5-diazatricyclo[7.2.1.0<sup>sup</sup>2<sup>sup</sup>.sup 7]dodeca-2,4,6-triene (13), whose potency and selectivity approached those of trimethoprim, a drug commonly used to treat *P. carinii* and *T. gondii* infection. 3,5-Diamino-4,6-diazatricyclo[6.2.1.0<sup>sup</sup>2<sup>sup</sup>.sup 7]undeca-2,4,6-triene (14), the analog of 13 with a one-carbon rather than a two-carbon bridge showed similar potency and selectivity against the *T. gondii* enzyme, but was a weak and nonselective inhibitor of *P. carinii* dihydrofolate reductase. The other compounds tested were likewise weak and nonselective.

### **Occurrence of an incomplete C8 molecule in homozygous C8 deficiency in man**

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Journal of Experimental Medicine (United States) 1981, 154/5 (1599-1607)

Sera from three unrelated individuals with recurrent Neisserial infections lacked C8 hemolytic activity, but contained a protein that is antigenically related to C8. Immunochemical analysis revealed complete identity of the C8-related protein of all three sera and a marked antigenic deficiency compared with normal C8. The C8-related protein was isolated from serum by adsorption to immobilized anti-C8 IgG, elution with 3 M guanidine, and subsequent gel filtration. Upon sodium dodecyl sulfate-polyacrylamide gel electrophoresis analysis, the abnormal protein resembled the alpha-gamma subunit of normal C8 with respect to mobility and its ability to be cleaved upon reduction into the alpha and gamma chains. The beta chain present in C8 was absent. Sedimentation equilibrium analysis indicated a molecular weight of 86,000 for the abnormal C8 protein, which is identical to that of the alpha-gamma subunit of normal C8. Amino acid analysis revealed no significant difference between the abnormal C8 and normal alpha-gamma. Unlike normal C8, the abnormal protein did not bind to EAC1-7 or to SC5b-7; however, upon addition to the deficient serum of beta chain isolated from normal C8, hemolytic activity was restored and formation of SC5b-9 occurred. We concluded that the dysfunctional C8 protein in the three individuals' serum is identical to the alpha-gamma subunit of normal C8 and that this form of C8 deficiency is distinct from the C8 deficiencies previously reported in which the entire three-chain protein is lacking.

### **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**

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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 H<sub>2</sub>O<sub>2</sub>, 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 H<sub>2</sub>O<sub>2</sub> produced. The more significant the inhibition of the coating to bacterial growth, the greater the amount of H<sub>2</sub>O<sub>2</sub> production. In addition, the bacterial survival rates on the surfaces of coatings were almost zero when H<sub>2</sub>O<sub>2</sub> was produced in amounts greater than 10<sup>-6</sup> mmol/cm<sup>2</sup>. However, the dominant concentrations of metal ions dissolved from coatings were outside of the bacterial lethal range.

### **Comparison of a topical benzoyl peroxide gel, oral minocycline, oral doxycycline and a combination for suppression of P. acnes in acne patients**

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Journal of Dermatological Treatment (United Kingdom), 1998, 9/3 (187-191)

Four groups of ten acne patients each received one of the following treatments for 1 month: (1) minocycline-'D', 100 mg twice daily; (2) doxycycline monohydrate, 100 mg twice daily; (3) 6% benzoyl peroxide-zinc gel twice daily; (4) minocycline-'D', 100 mg twice daily and 6% benzoyl peroxide-zinc gel twice daily. Suppression of Propionibacterium acnes was assessed by the detergent scrub method after 2 and 4 weeks of treatment. Minocycline-'D' had a far greater ability to suppress P. acnes than doxycycline. Minocycline-'D' resulted in almost a 2-log, decrease in P. acnes compared with less than 1-log decrease with doxycycline. Benzoyl peroxide-zinc gel was also more efficacious than doxy-cycline. As expected, the combination of minocycline-'D' and benzoyl peroxide-zinc gel was substantially more effective than the comparator treatments. The greater therapeutic efficacy of minocycline-'D' in acne cannot be fully explained by its antibacterial activity. Evidence is presented to show that minocycline has a wide spectrum of pharmacologic activities, including antiinflammatory effects, which explains its increasing therapeutic applications in a variety of unrelated disorders.

### **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.

### **Anti-inflammatory activity in rats and mice of phenolic acids isolated from *Scrophularia frutescens***

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Journal of Pharmacy and Pharmacology (United Kingdom), 1998, 50/10 (1183-1186)

Different species of the *Scrophularia* genus (*Scrophulariaceae*) have been reported to have bacteriostatic and anti-inflammatory properties. In previous studies the anti-inflammatory and antibacterial activity of different extracts from *Scrophularia frutescens* were investigated and p-coumaric, caffeic, ferulic gentisic, protocatechuic, syringic and isovanillic acids were isolated and identified. In this work the anti-inflammatory activity of these compounds, administered orally, has been studied against carrageenan-induced rat paw oedema and, administered topically, against tetradecanoylphorbol acetate (TPA)-induced mouse ear oedema. The compounds' myeloperoxidase activity in inflamed ear was also investigated. Some of the phenolic acids were remarkably active in the TPA test (protocatechuic 71.59% inhibition, < 0.001; syringic 74.43%, < 0.001; ferulic 71.02% < 0.001) and all significantly inhibited mouse ear oedema. They were only moderately active, or were without activity, in the carrageenan test. These results imply that the phenolic acids assayed are more effective topically than as oral anti-inflammatory agents and that their action is markedly influenced by the inhibition of neutrophil migration into inflamed tissue. This study has also enabled us to make some observations on the possible relationship between the chemical structure and anti-inflammatory activity of the compounds assayed.

### **Effects of bacterial DNA on cytokine production by (NZB/NZW)F1 mice**

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Journal of Immunology (United States), 1998, 161/8 (3890-3895)

Microbial DNA has multiple immune effects including the Capacity to induce polyclonal B cell activation and cytokine production in normal mice. We recently described the accelerated induction of anti-DNA Abs in NZB/NZW mice immunized with *Escherichia coli* (EC) dsDNA; paradoxically these mice developed less renal disease than unimmunized mice or mice immunized with calf thymus DNA. We postulated that alterations in cytokine production induced by bacterial DNA may play a key role in renal protection. To determine the effect of bacterial DNA on cytokine production in NZB/NZW mice, we measured the serum cytokine levels, cell culture supernatant cytokine levels, and number of cytokine-producing splenocytes in NZB/NZW mice injected with EC DNA, calf thymus DNA, or an immune active oligonucleotide. There was a 10- to 25-fold increase in the number of cells secreting IFN-gamma compared with IL-4 in mice immunized with EC DNA. IL-12-secreting cells were also increased by bacterial DNA immunization. In parallel with the increase in IFN-gamma secreting cells, there was a significant rise in serum IFN-gamma levels in mice receiving EC DNA. These results indicate that EC DNA modulates systemic cytokine levels in NZB/NZW mice, selectively increasing IL-12 and IFN-gamma while decreasing IL-4 production. The cytokine response of NZB/NZW mice to bacterial DNA may be of significance in disease pathogenesis and relevant to the treatment of lupus-like disease.

### **Screening of oriental herbal medicines for antibacterial activities**

O Sung Bae; Jae Ock Hwang; Duk Kyun Ahn; Woo E.-R.; Seon Hee Seo; Hyoungh 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.

### **Surveillance of susceptibility of clinical isolates of various bacterial species to antibacterial agents**

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Japanese Journal of Chemotherapy (Japan), 1998, 46/9 (343-363)

We used agar-dilution MIC determination to assess the activity of various antibacterial agents against clinical isolates (20 Gram negative aerobic bacteria, 1,178 strains), which were isolated in 1996 at 16 facilities in Japan and compared the results with those of similar study in 1992 and 1994. Most cepheems, carbapenems (CBPs), aztreonam, aminoglycosides (AGs) and new quinolones (NQs) exhibited high antibacterial activity against *Escherichia coli*, *Klebsiella* spp., *Proteus* spp. and *Morganella morganii* with an MIC<sub>90</sub> of less than 3.13 microg/ml. However, several strains highly resistant to NQs appeared among most bacterial species. One



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.,  $2 \times 10^{-8}$  to  $2 \times 10^{-6}$  M); however, at the higher concentrations (i.e.,  $2 \times 10^{-8}$  to  $2 \times 10^{-6}$  M range) the predominant effect was the inhibition of the metabolism of AFBsub 1 to its mutagenic metabolites. Vitamin E was more potent in inhibiting the expression of AFBsub 1-induced mutagenesis than vitamin C. However, the major inhibitory effects of vitamin E were related to the metabolism of AFBsub 1, whereas vitamin C was inhibitory at both metabolic and the post-metabolic levels of the AFBsub 1 mutagenesis assay. The results of these investigations suggest that vitamins A, C, or E inhibit both AFBsub 1 metabolism to its mutagenic metabolites as well as the expression of AFBsub 1-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 10<sup>5</sup> *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<sup>-5</sup> M and when added before infection at the physiologic concentration of 10<sup>-7</sup> 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 log<sub>10</sub> 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 75degr.C for 30 min has been found.

## **Effect of compounds with antibacterial activities in human milk on respiratory syncytial virus and cytomegalovirus in vitro**

Portelli J.; Gordon A.; May J.T. Dr. J.T. May, School of Microbiology, LaTrobe University, Bundoora, Vic. 3083 Australia

Journal of Medical Microbiology (United Kingdom), 1998, 47/11 (1015-1018)

The effect of some antibacterial compounds present in human milk were tested for antiviral activity against respiratory syncytial virus, Semliki Forest virus and cytomegalovirus. These included the gangliosides GM1, GM2 and GM3, sialyl-lactose, lactoferrin and chondroitin sulphate A, B and C, which were all tested for their ability to inhibit the viruses in cell culture. Of the compounds tested, only the ganglioside GM2, chondroitin sulphate B and lactoferrin inhibited the absorption and growth of respiratory syncytial virus in cell culture, and none inhibited the growth of Semliki Forest virus, indicating that lipid antiviral activity was not associated with any of the gangliosides. While the concentrations of these two compounds required to inhibit respiratory syncytial virus were in excess of those present in human milk, sialyl-lactose concentrations similar to those present in human milk increased the growth of cytomegalovirus. Lactoferrin was confirmed as inhibiting both respiratory syncytial virus and cytomegalovirus growth in culture even when used at lower concentrations than those present in human milk. The antiviral activities of GM2, chondroitin sulphate B and lactoferrin were tested when added to an infant formula. Lactoferrin continued to have antiviral activity against cytomegalovirus, but a lower activity against respiratory syncytial virus; ganglioside GM2 and chondroitin sulphate B still maintained antiviral activity against respiratory syncytial virus.

## **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.**

Kruzel ML, Harari Y, Chen CY, Castro GA. Department of Integrative Biology and Pharmacology, University of Texas, Houston Health Science Center, 77225, USA.

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.

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