

Common Cold
Updated: 08/26/2004

ABSTRACTS

A strategic call to utilize Echinacea-garlic in flu-cold seasons.

Abdullah T.

J Natl Med Assoc. 2000 Jan; 92(1):48-51.

Zinc lozenges reduce the duration of common cold symptoms.

Anon.

Nutr Rev. 1997; 55(3):82-5.

Comparison of oral and aerosol ribavirin regimens in the high risk elderly.

Bernstein JM, Liss H, Erk SD.

J Clin Pharmacol. 1989 Dec; 29(12):1128-34.

A comparison of different regimens of ribavirin (R), administered either orally or by aerosol, was performed in 16 elderly subjects (13 men, 3 women, mean age 63 +/- 8 years) considered to be in the "high-risk" category for complications from influenza as defined by the Centers for Disease Control. The subjects were divided into four groups. Group O-600 received 600 mg orally R every 8 hours for 48 hours followed by 200 mg every 8 hours for 72 hours for a total dose of 5.4 g (22.1 mmol). Group O-800 received 800 mg oral R every 8 hours for 24 hours followed by 400 mg every 12 hours for 96 hours for a total dose of 4.1 g (22.9 mMoles). Group A-40 received R (40 mg/ml) aerosolized through a small particle aerosol generator for 6 hours every 12 hours for 96 hours, yielding an average delivered dose of 6.2 g (25.4 mMoles) R. Group A-60 received aerosolized R (60 mg/mL) for 2 hours every 8 hours for 96 hours, yielding an average delivered dose of 4.6 g (18.8 mMoles) R. No hematologic or other laboratory abnormalities were associated with any of the regimens. Group O-800 and O-600 reached mean peak plasma R levels of 11.8 microM and 5.3 microM, respectively, after 18 hours of therapy. Subsequent administration of 20 mg R every 8 hours was sufficient to maintain a plasma R level greater than 7 microM. Among the aerosol groups, group A-40 approached steady state plasma R levels (8-10 microM) more quickly than group A-60.(ABSTRACT TRUNCATED AT 250 WORDS)

Prospects of the clinical utilization of melatonin.

Bubenik GA, Blask DE, Brown GM, et al.

Biol Signals Recept. 1998 Jul; 7(4):195-219.

This review summarizes the present knowledge on melatonin in several areas on physiology and discusses various prospects of its clinical utilization. Ever increasing evidence indicates that melatonin has an immuno-hematopoietic role. In animal studies, melatonin provided protection against gram-negative septic shock, prevented stress-induced immunodepression, and restored immune function after a hemorrhagic shock. In human studies, melatonin amplified the antitumoral activity of interleukin-2. Melatonin has been proven as a powerful cytostatic drug in vitro as well as in vivo. In the human clinical field, melatonin appears to be a promising agent either as a diagnostic or prognostic marker of neoplastic diseases or as a compound used either alone or in combination with the standard cancer treatment. Utilization of melatonin for treatment of rhythm disorders, such as those manifested in jet lag, shift work or blindness, is one of the oldest and the most successful clinical application of this chemical. Low doses of melatonin applied in controlled-release preparation were very effective in improving the sleep latency, increasing the sleep efficiency and rising sleep quality scores in elderly, melatonin-deficient insomniacs. In the cardiovascular system, melatonin seems to regulate the tone of cerebral arteries; melatonin receptors in vascular beds appear to participate in the regulation of body temperature. Heat loss may be the principal mechanism in the initiation of sleepiness caused by melatonin. The role of melatonin in the development of migraine headaches is at present uncertain but more research could result in new

ways of treatment. Melatonin is the major messenger of light-dependent periodicity, implicated in the seasonal reproduction of animals and pubertal development in humans. Multiple receptor sites detected in brain and gonadal tissues of birds and mammals of both sexes indicate that melatonin exerts a direct effect on the vertebrate reproductive organs. In a clinical study, melatonin has been used successfully as an effective female contraceptive with little side effects. Melatonin is one of the most powerful scavengers of free radicals. Because it easily penetrates the blood-brain barrier, this antioxidant may, in the future, be used for the treatment of Alzheimer's and Parkinson's diseases, stroke, nitric oxide, neurotoxicity and hyperbaric oxygen exposure. In the digestive tract, melatonin reduced the incidence and severity of gastric ulcers and prevented severe symptoms of colitis, such as mucosal lesions and diarrhea

Use of visual analogue scale measurements (VAS) to assess the effectiveness of standardized *Andrographis paniculata* extract SHA-10 in reducing the symptoms of common cold. A randomized double blind-placebo study.

Caceres DD, Hancke JL, Burgos RA, et al.

Phytomedicine. 1999 Oct; 6(4):217-23.

The objective of our study was to measure the effectiveness of *Andrographis paniculata* SHA-10 extract in reducing the prevalence and intensity of symptoms and signs of common cold as compared with a placebo. A group of 158 adult patients of both sexes completed the randomized double blind study in Valdivia, Chile. The patients were divided in two equal size groups, one of which received *Andrographis paniculata* dried extract (1200 mg/day) and the other a placebo during a period of 5 days. Evaluations for efficacy were performed by the patient at day 0, 2, and 4 of the treatment; each completed a self-evaluation (VAS) sheet with the following parameters: headache, tiredness, earache, sleeplessness, sore throat, nasal secretion, phlegm, frequency and intensity of cough. In order to quantify the magnitude of the reduction in the prevalence and intensity of the signs and symptoms of common cold, the risk (Odds Ratio = OR) was calculated using a logistic regression model. At day 2 of treatment a significant decrease in the intensity of the symptoms of tiredness (OR = 1.28; 95% CI 1.07-1.53), sleeplessness (OR = 1.71; 95% CI 1.38-2.11), sore throat (OR = 2.3; 95% CI 1.69-3.14) and nasal secretion (OR = 2.51; 95% CI 1.82-3.46) was observed in the *Andrographis* SHA-10 group as compared with the placebo group. At day 4, a significant decrease in the intensity of all symptoms was observed for the *Andrographis paniculata* group. The higher OR values were for the following parameters: sore throat (OR = 3.59; 95% CI 2.04-5.35), nasal secretion (OR = 3.27; 95% CI 2.31-4.62) and earache (OR = 3.11; 95% CI 2.01-4.80) for *Andrographis paniculata* treatment over placebo, respectively. It is concluded that *Andrographis paniculata* had a high degree of effectiveness in reducing the prevalence and intensity of the symptoms in uncomplicated common cold beginning at day two of treatment. No adverse effects were observed or reported

Psychological stress, cytokine production, and severity of upper respiratory illness.

Cohen S, Doyle WJ, Skoner DP.

Psychosom Med. 1999 Mar; 61(2):175-80.

OBJECTIVE: The purpose of this study is to assess the role of psychological stress in the expression of illness among infected subjects and to test the plausibility of local proinflammatory cytokine production as a pathway linking stress to illness. **METHODS:** After completing a measure of psychological stress, 55 subjects were experimentally infected with an influenza A virus. Subjects were monitored in quarantine daily for upper respiratory symptoms, mucus production, and nasal lavage levels of interleukin (IL)-6. **RESULTS:** Higher psychological stress assessed before the viral challenge was associated with greater symptom scores, greater mucus weights, and higher IL-6 lavage concentrations in response to infection. The IL-6 response was temporally related to the two markers of illness severity, and mediation analyses indicated that these data were consistent with IL-6 acting as a major pathway through which stress was associated with increased symptoms of illness. However, this pattern of data is also consistent with increases in IL-6 occurring in response to tissue damage associated with illness symptoms. **CONCLUSIONS:** Psychological stress predicts a greater expression of illness and an increased production of IL-6 in response to an upper respiratory infection

[Effect of *Astragalus membranaceus* on Ca²⁺ influx and coxsackie virus B3 RNA replication in cultured neonatal rat heart cells].

Guo Q, Peng TQ, Yang YZ.

Zhongguo Zhong Xi Yi Jie He Za Zhi. 1995 Aug; 15(8):483-5.

The effect of *Astragalus membranaceus* (AM) on Ca²⁺ influx across the myocardial plasma membrane and coxsackie virus B3 (CVB3)-RNA replication in cultured neonatal rat heart cells infected with CVB3 was investigated. It was found that the Ca²⁺ influx could be inhibited significantly (P < 0.01) by AM after infection of heart cells for 48 h. In addition, when the cultured heart cells infected with CVB3 and treated with AM for 48 h, the Ca²⁺ influx of infected heart cells also could be inhibited by AM (P < 0.05) and the amounts of CVB3-RNA in myocytes were significantly decreased than that in infected control group (P < 0.001).

These phenomena suggested that AM could exert the effects of decreasing secondary Ca²⁺ damages, and improving the abnormal myocardial electric activity, and inhibiting replication of CVB3-RNA in myocardium. Thus, it is a rational choice to treat patients with AM in viral myocarditis

Antiviral effects of plasma and milk proteins: lactoferrin shows potent activity against both human immunodeficiency virus and human cytomegalovirus replication in vitro.

Harmsen MC, Swart PJ, de Bethune MP, et al.

J Infect Dis. 1995 Aug; 172(2):380-8.

Native and chemically derivatized proteins purified from serum and milk were assayed in vitro to assess their inhibiting capacity on the cytopathic effect of human immunodeficiency virus (HIV)-1 and human cytomegalovirus (HCMV) on MT4 cells and fibroblasts, respectively. Only native and conformationally intact lactoferrin from bovine or human milk, colostrum, or serum could completely block HCMV infection (IC₅₀ = 35-100 micrograms/mL). Moreover, native lactoferrin also inhibited the HIV-1-induced cytopathic effect (IC₅₀ = 40 micrograms/mL). When negatively charged groups were added to lactoferrin by succinylation, there was a 4-fold stronger antiviral effect on HIV-1, but the antiviral potency for HCMV infection was mostly decreased. Lactoferrin likely exerts its effect at the level of virus adsorption or penetration (or both), because after HCMV penetrated fibroblasts, the ongoing infection could not be further inhibited

Effectiveness and safety of intranasal ipratropium bromide in common colds. A randomized, double-blind, placebo-controlled trial.

Hayden FG, Diamond L, Wood PB, et al.

Ann Intern Med. 1996 Jul 15; 125(2):89-97.

OBJECTIVE. To determine the tolerability and clinical effectiveness of intranasal ipratropium bromide for the treatment of symptoms of common colds. **DESIGN.** Multicenter, double-blind, randomized trial. **SETTING.** 3 university student health services. **PATIENTS.** 411 previously healthy persons 14 to 56 years of age who had cold symptoms that had lasted for no more than 36 hours, rhinorrhea subjectively judged to be of at least moderate severity, and documented nasal discharge of at least 1.5 g over a 1-hour observation period. **INTERVENTION.** Either 1) ipratropium bromide nasal spray 0.06% in buffered salt solution, two 42-micrograms sprays per nostril administered by metered pump spray; 2) control nasal spray, which consisted of buffered salt solution; or 3) no treatment. Treatments were self-administered three or four times daily during waking hours for 4 days. After receiving their morning dose, patients stayed at the study center for 6 hours on study day 1 and 3 hours on study day 2; symptom severity was recorded and nasal mucus discharges were collected and weighed hourly during these periods. **RESULTS.** Ipratropium recipients had 26% less nasal discharge than controls (P = 0.0024) and 34% less nasal discharge than untreated patients (P = 0.0001). Severity of rhinorrhea as judged subjectively was reduced in ipratropium recipients by 31% compared with controls and by 78% compared with untreated patients (P = 0.0001 for both comparisons). In addition to being associated with reductions in daily assessments of the severity of rhinorrhea (P < or = "0.003)," ipratropium was associated with reduced sneezing on study days 2 (20% difference; P = "0.03") and 4 (30% difference; P = "0.02") but not with reduced nasal congestion compared with the control spray. Ipratropium was generally well tolerated but was associated with higher rates of blood-tinged mucus (16.8% in the ipratropium group compared with 3.6% in the control group; P = "0.01") and nasal dryness (11.7% in the ipratropium group compared with 3.6% in the control group; P = "0.021") than the control spray. Patient assessments of the overall effectiveness of treatment were more favorable for ipratropium than for the control spray (P < or = "0.026") or for no treatment (P < or = "0.002") on each day of inquiry (study days 1, 2, and 5). **CONCLUSIONS.** Intranasal ipratropium bromide provides specific relief of rhinorrhea and sneezing associated with common colds

Vitamin C and common cold incidence: a review of studies with subjects under heavy physical stress.

Hemila H.

Int J Sports Med. 1996 Jul; 17(5):379-83.

Several studies have observed an increased risk of respiratory infections in subjects doing heavy physical exercise. Vitamin C has been shown to affect some parts of the immune system, and accordingly it seems biologically conceivable that it could have effects on the increased incidence of respiratory infections caused by heavy physical stress. In this report the results of three placebo-controlled studies that have examined the effect of vitamin C supplementation on common cold incidence in subjects under acute physical stress are analyzed. In one study the subjects were school-children at a skiing camp in the Swiss Alps, in another they were military troops training in Northern Canada, and in the third they were participants in a 90 km running race. In each of the three studies a considerable reduction in common cold incidence in the group supplemented with vitamin C(0.6-1.0 g/day) was found. The pooled rate ratio (RR) of common cold infections in the studies was 0.50 (95% CI: 0.35-0.69) in favour of

vitamin C groups. Accordingly, the results of the three studies suggest that vitamin C supplementation may be beneficial for some of the subjects doing heavy exercise who have problems with frequent upper respiratory infections

Vitamin C intake and susceptibility to the common cold.

Hemila H.

Br J Nutr. 1997 Jan; 77(1):59-72.

Although the role of vitamin C in common cold incidence had been studied extensively, the level of vitamin C intake has not been unequivocally shown to affect the incidence of colds. In the present study the six largest vitamin C supplementation (≥ 1 g/d) studies, including over 5000 episodes in all, have been analysed, and it is shown that common cold incidence is not reduced in the vitamin C-supplemented groups compared with the placebo groups (pooled rate ratio (RR) 0.99; 95% CI 0.93, 1.04). Consequently these six major studies give no evidence that high-dose vitamin C supplementation decreases common cold incidence in ordinary people. Nevertheless, the analysis was continued with the hypothesis that vitamin C intake may affect common cold susceptibility in specific groups of people. It was assumed that the potential effect of supplementation might be most conspicuous in subjects with low dietary vitamin C intake. The average vitamin C intake has been rather low in the UK and plasma vitamin C concentrations are in general lower in males than in females. In four studies with British females vitamin C supplementation had no marked effect on common cold incidence (pooled RR 0.95; 95% CI 0.86, 1.04). However, in four studies with British male schoolchildren and students a statistically highly significant reduction in common cold incidence was found in groups supplemented with vitamin C (pooled RR 0.70; 95% CI 0.60, 0.81). Thus, these studies with British males indicate that vitamin C intake has physiological effects on susceptibility to common cold infections, although the effect seems quantitatively meaningful only in limited groups of people and is not very large

Vitamin C supplementation and the common cold--was Linus Pauling right or wrong?

Hemila H.

Int J Vitam Nutr Res. 1997; 67(5):329-35.

In 1970 Linus Pauling claimed that vitamin C prevents and alleviates the episodes of the common cold. Pauling was correct in concluding from trials published up till then, that in general vitamin C does have biological effects on the common cold, but he was rather over-optimistic as regards the size of benefit. His quantitative conclusions were based on a single placebo-controlled trial on schoolchildren in a skiing camp in the Swiss Alps, in which a significant decrease in common cold incidence and duration in the group administered 1 g/day of vitamin C was found. As children in a skiing camp are not a representative sample of the general population, Pauling's extrapolation to the population at large was too bold, erring as to the magnitude of the effect. Nevertheless, Pauling's general conclusion that vitamin C has physiological effects on the common cold is of major importance as it conflicts with the prevailing consensus that the only physiological effect of vitamin C on human beings is to prevent scurvy

Melatonin.

Kostogloy-Athanassiou I.

Arch Hellenic Med. 1998; 15(3):281-306.

[The effect of astragalus polysaccharides (APS) on cell mediated immunity (CMI) in burned mice].

Liang H, Zhang Y, Geng B.

Zhonghua Zheng Xing Shao Shang Wai Ke Za Zhi. 1994 Mar; 10(2):138-41.

In this paper, the changes in CMI in mice were determined after burn injury, and the effects of APS on CMI of burned mice were investigated in vivo. The results showed that on day 6 postburn, spleen index and thymus index were reduced, T lymphocyte transformation and interleukin 2 (IL-2) production were suppressed. Furthermore, the serum and macrophages from burned mice showed significant suppressive activity upon T lymphocyte transformation in vitro, and suppressive index (SI) of suppressor T cell (Ts) was greater than that of normal controls. Intraperitoneal administration of APS (250mg/kg daily, from day 0 to 5 could restore spleen index and thymus index of burned mice, reverse the suppression of T lymphocyte transformation and IL-2 production, reduce remarkably the suppressive activity of serum, macrophages and Ts. It is suggested that (1) burn injury-induced suppression of CMI may be related to the augmented suppressive activity of serum, macrophages and Ts; (2) administration of APS may restore the impaired CMI after burn injury by reducing the suppressive activity of postburn serum, macrophages and Ts

Endocrine and immune effects of melatonin therapy in metastatic cancer patients.

Lissoni P, Barni S, Crispino S, et al.

Eur J Cancer Clin Oncol. 1989 May; 25(5):789-95.

Melatonin, the most important indole hormone produced by the pineal gland, appears to inhibit tumor growth; moreover, altered melatonin secretion has been reported in cancer patients. Despite these data, the possible use of melatonin in human neoplasms remains to be established. The aim of this clinical trial was to evaluate the therapeutic, immunological and endocrine effects of melatonin in patients with metastatic solid tumor, who did not respond to standard therapies. The study was carried out on 14 cancer patients (colon, six; lung, three; pancreas, two; liver, two; stomach, one). Melatonin was given intramuscularly at a daily dose of 20 mg at 3.00 p.m., followed by a maintenance period in an oral dose of 10 mg daily in patients who had a remission, stable disease or an improvement in PS. Before and after the first 2 months of therapy, GH, somatomedin-C, beta-endorphin, melatonin blood levels and lymphocyte subpopulations were evaluated. A partial response was achieved in one case with cancer of the pancreas, with a duration of 18+ months; moreover, six patients had stable disease, while the other eight progressed. An evident improvement in PS was obtained in 8/14 patients. In patients who did not progress, T4/T8 mean ratio was significantly higher after than before melatonin therapy, while it decreased in patients who progressed. On the contrary, hormonal levels were not affected by melatonin administration. This study would suggest that melatonin may be of value in untreatable metastatic cancer patients, particularly in improving their PS and quality of life; moreover, based on its effects on the immune system, melatonin could be tested in association with other antitumor treatments

Pineal-opioid system interactions in the control of immunoinflammatory responses.

Lissoni P, Barni S, Tancini G, et al.

Ann N Y Acad Sci. 1994 Nov 25; 741:191-6.

Several studies have demonstrated involvement of the pineal gland in the regulation of neuropeptide secretion and activity. In particular, the existence of links between the pineal gland and the brain opioid system has been documented. Both opioid peptides and melatonin (MLT), the most investigated pineal hormone, play an important role in neuromodulation of the immunity. Moreover, the immune effects of MLT are mediated by endogenous opioid peptides, which may be produced by both the endocrine system and the immune cells. In addition, the immune dysfunctions that characterize some human diseases, such as cancer, depend not only on the immune system per se, but also at least in part, on altered secretion of immunomodulating neurohormones, including MLT and opioid peptides. Therefore, the exogenous administration of neurohormones could potentially improve the immune status in humans. The present study evaluates the effects of MLT on changes in the number of T lymphocytes, natural killer cells, and eosinophils induced by exogenous administration of interleukin-2 (IL-2). Macrophage activity was also evaluated by determining serum levels of its specific marker, neopterin. The study was performed in 90 patients with advanced solid neoplasms, who received IL-2 at a dose of 3 million IU/day subcutaneously for 6 days a week for 4 weeks plus MLT at a daily dose of 40 mg. Both drugs were given in the evening. The results were compared to those in 40 cancer patients treated with IL-2 alone. The mean increase in T lymphocytes, natural killer cells, and eosinophils was significantly higher in patients treated with IL-2 plus MLT than in those who received IL-2 alone.(ABSTRACT TRUNCATED AT 250 WORDS)

Immunoendocrine therapy with low-dose subcutaneous interleukin-2 plus melatonin of locally advanced or metastatic endocrine tumors.

Lissoni P, Barni S, Tancini G, et al.

Oncology. 1995 Mar; 52(2):163-6.

Recent evidence has shown that endocrine tumors are under an endocrine and an immune regulation, and that biotherapies with interferon or the long-acting somatostatin analog octreotide may be effective in the control of tumor growth and clinical symptomatology. Within the biotherapies of tumors, interleukin-2(IL-2) has appeared to play an essential role in the antitumor immune response. Despite its important antitumor role, very few studies have been carried out to investigate the possible use of IL-2 in the treatment of advanced endocrine tumors. Its potential toxicity would represent the main limiting factor for the clinical experiments with IL-2. Our previous studies have shown that the pineal hormone melatonin (MLT) may amplify the antitumor activity of IL-2, either through immunomodulating mechanisms or through a direct cytostatic activity by inhibiting tumor growth factor production. On this basis, we have performed a phase II pilot study with low-dose IL-2 plus MLT in 14 patients with untreatable endocrine tumors because of disseminated disease, lack of response to previous standard biotherapies or chemotherapies, or tumors for whom no effective therapy is available. Thyroid cancers, carcinoid and endocrine pancreatic tumors were the most frequent neoplasms. IL-2 was given at 3 million IU/day s.c. at 8 p.m. for 6 days/week for 4 weeks, corresponding to one cycle. MLT was given orally at 40 mg/day at 8 p.m. every day. In nonprogressed patients, a second cycle

was given after a 21-day rest period. Patients were considered as evaluable when they received at least one complete cycle, and 12 patients were fully evaluable. According to WHO criteria, a partial response was achieved in 3/12 (25%) patients (carcinoid tumor: 1; neuroendocrine lung tumor: 1; pancreatic islet cell tumor: 1). Another patient with gastrinoma had a more than 50% reduction of tumor markers. Toxicity was low in all patients. This preliminary study suggests that low-dose IL-2 immunotherapy in association with the pineal hormone MLT may constitute a new well-tolerated and potentially active therapy of untreatable advanced endocrine tumors

Macrophage activation by the polysaccharide arabinogalactan isolated from plant cell cultures of *Echinacea purpurea*.

Luettig B, Steinmuller C, Gifford GE, et al.

J Natl Cancer Inst. 1989 May 3; 81(9):669-75.

In this study, acidic arabinogalactan, a highly purified polysaccharide from plant cell cultures of *Echinacea purpurea*, with a molecular weight of 75,000, was effective in activating macrophages to cytotoxicity against tumor cells and micro-organisms (*Leishmania enriettii*). Furthermore, this polysaccharide induced macrophages to produce tumor necrosis factor (TNF-alpha), interleukin-1 (IL-1), and interferon-beta 2. Arabinogalactan did not activate B cells and did not induce T cells to produce interleukin-2, interferon-beta 2, or interferon-gamma, but it did induce a slight increase in T-cell proliferation. When injected ip, this agent stimulated macrophages, a finding that may have therapeutic implications in the defense against tumors and infectious diseases

The immunoneuroendocrine role of melatonin.

Maestroni GJ.

J Pineal Res. 1993 Jan; 14(1):1-10.

A tight, physiological link between the pineal gland and the immune system is emerging from a series of experimental studies. This link might reflect the evolutionary connection between self-recognition and reproduction. Pinealectomy or other experimental methods which inhibit melatonin synthesis and secretion induce a state of immunodepression which is counteracted by melatonin. In general, melatonin seems to have an immunoenhancing effect that is particularly apparent in immunodepressive states. The negative effect of acute stress or immunosuppressive pharmacological treatments on various immune parameters are counteracted by melatonin. It seems important to note that one of the main targets of melatonin is the thymus, i.e., the central organ of the immune system. The clinical use of melatonin as an immunotherapeutic agent seems promising in primary and secondary immunodeficiencies as well as in cancer immunotherapy. The immunoenhancing action of melatonin seems to be mediated by T-helper cell-derived opioid peptides as well as by lymphokines and, perhaps, by pituitary hormones. Melatonin-induced-immuno-opioids (MIIO) and lymphokines imply the presence of specific binding sites or melatonin receptors on cells of the immune system. On the other hand, lymphokines such as gamma-interferon and interleukin-2 as well as thymic hormones can modulate the synthesis of melatonin in the pineal gland. The pineal gland might thus be viewed as the crux of a sophisticated immunoneuroendocrine network which functions as an unconscious, diffuse sensory organ

T-helper-2 lymphocytes as a peripheral target of melatonin.

Maestroni GJ.

J Pineal Res. 1995 Mar; 18(2):84-9.

In the past several years we demonstrated that the pineal neurohormone melatonin has immunoenhancing properties and can counteract the immunodepression that may follow acute stress, drug treatment, and viral diseases or aging. Several laboratories have subsequently confirmed and extended our findings. It soon appeared evident that T-derived cytokines constitute the main mediators of the immunological effect of melatonin. We have recently found a high affinity (Kd: 346 +/- 24 pM) binding site for 125I-melatonin on T-helper-type 2 lymphocytes in the bone marrow. Activation of this putative melatonin receptor, with both physiological and pharmacological concentrations of melatonin, resulted in an enhanced production of interleukin-4 (IL4), which in turn acted on bone marrow stromal cells and induced the release of hematopoietic growth factors. This melatonin-cytokine cascade showed the remarkable capacity of rescuing hematopoietic functions in mice treated with cancer chemotherapeutic compounds without interfering with the anticancer action of these agents. The very low concentration (0.1 nM) at which melatonin is active may well reflect a physiological function of endogenous melatonin. The pineal gland has been, in fact, reported to signal the blood forming system. The evidence of IL4 involvement is relevant to our understanding of many melatonin effects and may be part of a pineal-immune axis involving also Th1 cytokines. The ability of rescuing hematopoiesis against the toxic action of cancer chemotherapeutic compounds and the presence of high-affinity IL4 receptors on human tumors provide a further promising rationale for the clinical use of melatonin

Double-blind, placebo-controlled pilot and phase III study of activity of standardized *Andrographis paniculata* Herba Nees extract fixed combination (Kan jang) in the treatment of uncomplicated upper-respiratory tract infection.

Melchior J, Spasov AA, Ostrovskij OV, et al.

Phytomedicine. 2000 Oct; 7(5):341-50.

Two randomized double-blind, placebo-controlled parallel group clinical trials were performed to investigate the effect of a standardized extract (SHA-10) of *Andrographis paniculata* fixed combination (Kan jang) in the treatment of uncomplicated upper-respiratory tract infections. 46 patients in the pilot study and 179 patients in the phase III study completed the study according to the protocol. Medication was taken three times daily for a minimum of 3 days and a maximum of 8 days for the pilot study, and for exactly three days in the phase III study. The primary outcome measures in the patients self-evaluation were: related to pain in the muscle, cough, throat symptoms, headache, nasal symptoms and eye symptoms and temperature. The physician's fixed score diagnosis was based mainly on sign/symptoms: ears, nose, oral cavity, lymph glands-tonsils and eyes. The total symptom score showed a tendency toward improvement in the pilot study ($p = 0,08$), while both the total symptom score and total diagnosis score showed highly significant improvement ($p < \text{or} = "0.0006"$ resp. 0.003) in the verum group as compared with the placebo. In both studies throat symptoms/signs, were found to show the most significant improvement

Zinc gluconate lozenges for treating the common cold. A randomized, double-blind, placebo-controlled study.

Mossad SB, Macknin ML, Medendorp SV, et al.

Ann Intern Med. 1996 Jul 15; 125(2):81-8.

BACKGROUND. The common cold is one of the most frequent human illnesses and is responsible for substantial morbidity and economic loss. No consistently effective therapy for the common cold has been well documented, but evidence suggests that several possible mechanisms may make zinc an effective treatment. **OBJECTIVE.** To test the efficacy of zinc gluconate lozenges in reducing the duration of symptoms caused by the common cold. **DESIGN.** Randomized, double-blind, placebo-controlled study. **SETTING.** Outpatient department of a large tertiary care center. **PATIENTS.** 100 employees of the Cleveland Clinic who developed symptoms of the common cold within 24 hours before enrollment. **INTERVENTION.** Patients in the zinc group ($n = 50$) received lozenges (one lozenge every 2 hours while awake) containing 13.3 mg of zinc from zinc gluconate as long as they had cold symptoms. Patients in the placebo group ($n = 50$) received similarly administered lozenges that contained 5% calcium lactate pentahydrate instead of zinc gluconate. **MAIN OUTCOME MEASURES.** Subjective daily symptom scores for cough, headache, hoarseness, muscle ache, nasal drainage, nasal congestion, scratchy throat, sore throat, sneezing, and fever (assessed by oral temperature). **RESULTS.** The time to complete resolution of symptoms was significantly shorter in the zinc group than in the placebo group (median, 4.4 days compared with 7.6 days; $P < 0.001$). The zinc group had significantly fewer days with coughing (median, 2.0 days compared with 4.5 days; $P = "0.04"$), headache (2.0 days and 3.0 days; $P = "0.02"$), hoarseness (2.0 days and 3.0 days; $P = "0.02"$), nasal congestion (4.0 days and 6.0 days; $P = "0.002"$), nasal drainage (4.0 days and 7.0 days; $P < 0.001$), and sore throat (1.0 day and 3.0 days; $P < 0.001$). The groups did not differ significantly in the resolution of fever, muscle ache, scratchy throat, or sneezing. More patients in the zinc group than in the placebo group had side effects (90% compared with 62%; $P < 0.001$), nausea (20% compared with 4%; $P = "0.02"$), and bad-taste reactions (80% compared with 30%; $P < 0.001$). **CONCLUSION.** Zinc gluconate in the form and dosage studied significantly reduced the duration of symptoms of the common cold. The mechanism of action of this substance in treating the common cold remains unknown. Individual patients must decide whether the possible beneficial effects of zinc gluconate on cold symptoms outweigh the possible adverse effects

The inhibitory effect of *astragalus membranaceus* on coxsackie B-3 virus RNA replication.

Peng T, Yang Y, Riesemann H, et al.

Chin Med Sci J. 1995 Sep; 10(3):146-50.

Using mice infected with coxsackie B-3 virus (CVB3) as a viral myocarditis model, we observed the inhibitory effect of *Astragalus membranaceus* (AM) on CVB3-RNA replication in myocardial tissue of mice by RNA-RNA in situ hybridization with negative-strand RNA probes labelled with 35S and quantitative imaging analysis of positive signals. The mechanism of its effect on CVB3-RNA replication has been investigated by detection of beta-interferon (beta-IFN) as well. Results showed that the copy numbers of CVB3-RNA as well as the histologic scores (necrosis) in myocardial tissues of infected-AM treated mice were significantly lower than those in infected and normal saline treated mice, suggesting that AM could inhibit the replication of CVB3-RNA, but its effect on CVB3-RNA replication had no correlation with induction of beta-IFN

Maitake Magic.

Preuss HMD.

2002;

Antiviral effect of bovine lactoferrin saturated with metal ions on early steps of human immunodeficiency virus type 1 infection.

Puddu P, Borghi P, Gessani S, et al.

Int J Biochem Cell Biol. 1998 Sep; 30(9):1055-62.

Lactoferrin is a mammalian iron-binding glycoprotein present in many biological secretions, such as milk, tears, semen and plasma and a major component of the specific granules of polymorphonuclear leucocytes. The effect of bovine lactoferrin (BLf) in apo-form or saturated with ferric, manganese or zinc ions, on human immunodeficiency virus type 1 (HIV-1) infection in the C8166 T-cell line was studied. Both HIV-1 replication and syncytium formation were efficiently inhibited, in a dose-dependent manner, by lactoferrins. BLf in apo and saturated forms markedly inhibited HIV-1 replication when added prior to HIV infection or during the virus adsorption step, thus suggesting a mechanism of action on the HIV binding to or entry into C8166 cells. Likewise, the addition of Fe³⁺+BLf prior to HIV infection and during the attachment step resulted in a marked reduction of the HIV-1 DNA in C8166 cells 20 h after infection. The potent antiviral effect and the high selectivity index exhibited by BLf suggest for this protein, in apo or saturated forms, an important role in inhibiting the early HIV-cell interaction, even though a post adsorption effect cannot be ruled out

Application of purified polysaccharides from cell cultures of the plant *Echinacea purpurea* to mice mediates protection against systemic infections with *Listeria monocytogenes* and *Candida albicans*.

Roesler J, Steinmuller C, Kiderlen A, et al.

Int J Immunopharmacol. 1991; 13(1):27-37.

Purified polysaccharides from cell cultures of the plant *Echinacea purpurea* were investigated for their ability to enhance phagocytes' activities regarding nonspecific immunity in vitro and in vivo. Macrophages (M phi) from different organ origin could be activated to produce IL-1, TNF alpha and IL-6, to produce elevated amounts of reactive oxygen intermediates and to inhibit growth of *Candida albicans* in vitro. Furthermore, in vivo the substances could induce increased proliferation of phagocytes in spleen and bone marrow and migration of granulocytes to the peripheral blood. These effects indeed resulted in excellent protection of mice against the consequences of lethal infections with one predominantly M phi dependent and one predominantly granulocyte dependent pathogen, *Listeria monocytogenes* and *C. albicans*, respectively. Specific immune responses to sheep red blood cells (antibody production) and to listeria (DTH) were not affected by the polysaccharides. The possibility of clinical use is discussed

Macrophage activation and induction of macrophage cytotoxicity by purified polysaccharide fractions from the plant *Echinacea purpurea*.

Stimpel M, Proksch A, Wagner H, et al.

Infect Immun. 1984 Dec; 46(3):845-9.

Purified polysaccharides (EPS) prepared from the plant *Echinacea purpurea* are shown to strongly activate macrophages. Macrophages activated with these substances develop pronounced extracellular cytotoxicity against tumor targets. The activation is brought about by EPS alone and is independent of any cooperative effect with lymphocytes. Also the production and secretion of oxygen radicals and interleukin 1 by macrophages is increased after activation with EPS. Cells of the macrophages lineage seem to be the main target for the action of these polysaccharides. EPS has no effect on T lymphocytes. B lymphocytes show a comparatively modest proliferation after incubation with *E. purpurea* EPS. Thus, these compounds, which are at least in tissue culture completely nontoxic, may be suited to activate in vivo cells of the macrophage system to cytotoxicity. They may therefore be of relevance in tumor and infectious systems

Antiviral activity of milk proteins: lactoferrin prevents rotavirus infection in the enterocyte-like cell line HT-29.

Superti F, Ammendolia MG, Valenti P, et al.

Med Microbiol Immunol (Berl). 1997 Oct; 186(2-3):83-91.

Different milk proteins were analyzed for their inhibitory effect on either rotavirus-mediated agglutination of human erythrocytes or rotavirus infection of the human enterocyte-like cell line HT-29. Proteins investigated were alpha-lactalbumin, beta-lactoglobulin, apo-lactoferrin, and Fe(3+)-lactoferrin, and their antiviral action was compared with the activity of mucin, a milk glycoprotein known to affect rotavirus infection. Results obtained demonstrated that beta-lactoglobulin, apo- and Fe(3+)-lactoferrin are able to inhibit the replication of rotavirus in a dose-dependent manner, apo-lactoferrin being the most active. It was shown that apo-lactoferrin hinders virus attachment to cell receptors since it is able to bind the viral particles and to prevent both rotavirus haemagglutination and viral binding to susceptible cells. Moreover, this protein markedly inhibited rotavirus antigen synthesis and yield in HT-29 cells when added during the viral adsorption step or when it was present in the first hours of infection, suggesting that this protein interferes with the early phases of rotavirus infection

Antiviral effects of milk proteins: acylation results in polyanionic compounds with potent activity against human immunodeficiency virus types 1 and 2 in vitro.

Swart PJ, Kuipers ME, Smit C, et al.

AIDS Res Hum Retroviruses. 1996 Jun 10; 12(9):769-75.

A number of native and modified milk proteins from bovine or human sources were analyzed for their inhibitory effects on human immunodeficiency virus type 1 (HIV-1) and HIV-2 in vitro in an MT4 cell test system. The proteins investigated were lactoferrin, alpha-lactalbumin, beta-lactoglobulin A, and beta-lactoglobulin B. By acylation of the amino function of the lysine residues in the proteins, using anhydrides of succinic acid or cis-aconitic acid, protein derivatives were obtained that all showed a strong antiviral activity against human immunodeficiency virus type 1 and/or 2. The in vitro IC₅₀ values of the aconitylated proteins were in the concentration range of 0.3 to 3 nM. Succinylation or aconitylation of alpha-lactalbumin and beta-lactoglobulin A/B also produced strong anti-HIV-2 activity with IC₅₀ values on the order 500 to 3000 nM. All compounds showed virtually no cytotoxicity at the concentration used. Peptide-scanning studies indicated that the native lactoferrin as well as the charged modified proteins strongly bind to the V3 loop of the gp120 envelope protein, with K_d values in the same concentration range as the above-mentioned IC₅₀. Therefore, shielding of this domain, resulting in inhibition of virus-cell fusion and entry of the virus into MT4 cells, may be the likely underlying mechanism of antiviral action

Lactoferrin. Antiviral activity of lactoferrin.

Swart PJ, Kuipers EM, Smit C, et al.

Adv Exp Med Biol. 1998; 443:205-13.

A series of native and chemically derivatized lactoferrins (Lfs) purified from milk and colostrum were assayed in vitro for their anti-HIV and anti-HCMV-cytopathic effects in MT4 cells and fibroblasts respectively. All Lfs from bovine and human milk or colostrum were able to completely block HCMV replication as well as inhibited HIV-1 induced cytopathic effects. Through acylation of the amino function of the lysine residues in Lf, using anhydrides of succinic acid or cis-aconitic acid, negatively charged Lf derivatives were obtained that all showed a strong antiviral activity against the HIV-1 in vitro. Acylated-Lf exhibited a 4-fold stronger antiviral effect on HIV-1 than the parent compound but the activity on HCMV was abolished. Peptide scanning studies indicated that the native Lf as well as acylated Lf strongly bind to the V3 domain of the HIV envelope protein gp120, with K_d values in the same concentration range as the in vitro IC₅₀. Therefore, shielding of this domain, resulting in inhibition of the virus-cell fusion and entry of the virus in MT4 cells is the likely mechanism underlying the anti-HIV activity. In contrast, addition of positive charges to Lf through amination of the proteins resulted in an increased anti-HCMV activity and a loss of anti-HIV activity, with anti-HCMV IC₅₀ values in the low micromolar concentration range. The N-terminal portion of LF appeared essential to this anti-HCMV effect. The specific distribution of positively and negatively charged domains in the molecule appears to be important in both the anti-HIV and anti-HCMV effects

Medicinal Mushrooms.

Tenney D.

1997;

Effect of *Astragalus membranaceus* injecta on Coxsackie B-2 virus infected rat beating heart cell culture.

Yang YZ, Guo Q, Jin PY, et al.

Chin Med J (Engl). 1987 Jul; 100(7):595-602.

Treatment of experimental Cocksackie B-3 viral myocarditis with Astragalus membranaceus in mice.

Yang YZ, Jin PY, Guo Q, et al.

Chin Med J (Engl). 1990 Jan; 103(1):14-8.

A murine model system for observing the effect of Astragalus Membranaceus (AM) on experimental myocarditis caused by Cocksackie B-3 virus (CB3V) was developed in 4-week-old male BALB/C mice. Gross, histopathologic and ultrastructural examinations of the infected-AM treated group showed that the severity and involved area of the myocardial lesions became milder and smaller than those in the infected-NS treated mice. The total lesion area, and the total lesion area/total myocardial area examined (%) and virus titer in the former group were also smaller and lower than those in the latter group. The results suggest that AM is effective in the inhibition of Cocksackie B virus propagation and protection of myocardium in mouse myocarditis

Inhibition of several strains of influenza virus in vitro and reduction of symptoms by an elderberry extract (*Sambucus nigra* L.) during an outbreak of influenza B Panama.

Zakay-Rones Z, Varsano N, Zlotnik M, et al.

J Altern Complement Med. 1995; 1(4):361-9.

A standardized elderberry extract, Sambucol (SAM), reduced hemagglutination and inhibited replication of human influenza viruses type A/Shangdong 9/93 (H3N2), A/Beijing 32/92 (H3N2), A/Texas 36/91 (H1N1), A/Singapore 6/86 (H1N1), type B/Panama 45/90, B/Yamagata 16/88, B/Ann Arbor 1/86, and of animal strains from Northern European swine and turkeys, A/Sw/Ger 2/81, A/Tur/Ger 3/91, and A/Sw/Ger 8533/91 in Madin-Darby canine kidney cells. A placebo-controlled, double blind study was carried out on a group of individuals living in an agricultural community (kibbutz) during an outbreak of influenza B/Panama in 1993. Fever, feeling of improvement, and complete cure were recorded during 6 days. Sera obtained in the acute and convalescent phases were tested for the presence of antibodies to influenza A, B, respiratory syncytial, and adenoviruses. Convalescent phase serologies showed higher mean and mean geometric hemagglutination inhibition (HI) titers to influenza B in the group treated with SAM than in the control group. A significant improvement of the symptoms, including fever, was seen in 93.3% of the cases in the SAM-treated group within 2 days, whereas in the control group 91.7% of the patients showed an improvement within 6 days ($p < 0.001$). A complete cure was achieved within 2 to 3 days in nearly 90% of the SAM-treated group and within at least 6 days in the placebo group ($p < 0.001$). No satisfactory medication to cure influenza type A and B is available. Considering the efficacy of the extract in vitro on all strains of influenza virus tested, the clinical results, its low cost, and absence of side-effects, this preparation could offer a possibility for safe treatment for influenza A and B

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