



Dr Paul Clayton examine the claims of other products:

Is Aloe Vera an immuno modulator?

A great many claims are made for Aloe Vera on the net by commercially motivated companies. Most of these reports are impossible to verify, as they have not been published in peer-reviewed journals. This deficiency is made very obvious by those sites that make claims, but do not cite the science – if any – behind the claims. A number of reports, however, have appeared in reputable journals and they do indeed show that some Aloe Vera extracts have immuno-stimulant properties.

For example, immuno-stimulation has been shown in vitro (Womble & Herlderman '92, Karaca et al '95, Egger et al '96, Zhang et al '96, Stuart et al '97, Ramamoorthy & Tizard '98, Lee et al '01), and in animal studies (Harris et al '91, Peng et al '91, Sheets et al '91, Usinger '97, Djeraba & Quere 2000).

This is a very small number of studies compared with the much more substantial body of work done on yeast-derived beta glucans. Furthermore, in comparative studies carried out by the Pentagon, Aloe Vera products were out-performed by the yeast extracts.

This was not entirely surprising. Despite the encouraging results reported in vitro and in animal studies, Aloe Vera was entirely ineffective in the treatment of patients with HIV / AIDS (Montaner et al '96). There has been at least one report showing that Aloe Vera preparations can in some cases cause the death of immune cells (Ramamoorthy & Tizard '98). And in one of the animal studies, while Aloe Vera boosted the immune response to heart worm (a parasite), it was totally ineffective in the face of viral challenge (Unsinger '97).

Even more worryingly, some excellent new work at the National Center for Natural Products Research at the University of Mississippi has shown that acemannan, the compound in Aloe Vera everyone thought was the immuno-stimulant, is completely ineffective (Pugh et al '01). The Mississippi group found that a different Aloe Vera compound, Aloeride, was responsible for the immuno-stimulating effects. This explains why the quality of Aloe Vera products is so variable; the manufacturing companies have been standardising their extracts incorrectly. And as Aloeride only accounts for 0.015% of the aloe juice dry weight, the slightest slip-up in the production method could mean a total loss of effectiveness.

Verdict

Aloe Vera contains a compound (Aloeride) which has strong immuno-stimulant properties. However, due to poor manufacturing technology and mistaken identity of the key active, Aloe Vera preparations are very variable. Until the manufacturing companies are able to offer Aloeride-standardised extracts, it would be unwise to rely on Aloe Vera as a treatment or prophylactic.

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REFERENCES

Djeraba A, Quere P. **In vivo macrophage activation in chickens with Acemannan, a complex carbohydrate extracted from Aloe vera.** Int J Immunopharmacol. 2000 May;22(5):365-72.

Egger SF, Brown GS, Kelsey LS, Yates KM, Rosenberg LJ, Talmadge JE. **Hematopoietic augmentation by a beta-(1,4)-linked mannan. Cancer Immunol Immunother.** 1996 Dec;43(4):195-205

Harris C, Pierce K, King G, Yates KM, Hall J, Tizard I. **Efficacy of acemannan in treatment of canine and feline spontaneous neoplasms.** Mol Biother. 1991 Dec;3(4):207-13.

Karaca K, Sharma JM, Nordgren R. **Nitric oxide production by chicken macrophages activated by Acemannan, a complex carbohydrate extracted from Aloe vera.** Int J Immunopharmacol. 1995 Mar;17(3):183-8.

Lee JK, Lee MK, Yun YP, Kim Y, Kim JS, Kim YS, Kim K, Han SS, Lee CK. **Acemannan purified from Aloe vera induces phenotypic and functional maturation of immature dendritic cells.** Int Immunopharmacol. 2001 Jul;1(7):1275-84.

Montaner JS, Gill J, Singer J, Raboud J, Arseneau R, McLean BD, Schechter MT, Ruedy J. **Double-blind placebo-controlled pilot trial of acemannan in advanced human immunodeficiency virus disease.** J Acquir Immune Defic Syndr Hum Retrovirol. 1996 Jun 1;12(2):153-7.

Peng SY, Norman J, Curtin G, Corrier D, McDaniel HR, Busbee D. **Decreased mortality of Norman murine sarcoma in mice treated with the immunomodulator, Acemannan.** Mol Biother. 1991 Jun;3(2):79-87

Pugh N, Ross SA, ElSohly MA, Pasco DS. Characterization of Aloeride, a new high-molecular-weight polysaccharide from Aloe vera with potent immunostimulatory activity. **J Agric Food Chem.** 2001 Feb;49(2):1030-4.

Ramamoorthy L, Kemp MC, Tizard IR. **Acemannan, a beta-(1,4)-acetylated mannan, induces nitric oxide production in macrophage cell line RAW 264.7.** Mol Pharmacol. 1996 Oct;50(4):878-84.

Sheets MA, Unger BA, Giggleman GF Jr, Tizard IR. **Studies of the effect of acemannan on retrovirus infections: clinical stabilization of feline leukemia virus-infected cats.** Mol Biother. 1991 Mar;3(1):41-5.

Stuart RW, Lefkowitz DL, Lincoln JA, Howard K, Gelderman MP, Lefkowitz SS. **Upregulation of phagocytosis and candidicidal activity of macrophages exposed to the immunostimulant acemannan.** Int J Immunopharmacol. 1997 Feb;19(2):75-82.

Usinger WR. **A comparison of antibody responses to veterinary vaccine antigens potentiated by different adjuvants.** Vaccine. 1997 Dec;15(17-18):1902-7.

Womble D, Helderman JH. **Enhancement of allo-responsiveness of human lymphocytes by acemannan (Carrisyn) Int J Immunopharmacol.** 1988;10(8):967-74

Womble D, Helderman JH. **The impact of acemannan on the generation and function of cytotoxic T-lymphocytes.** Immunopharmacol Immunotoxicol. 1992;14(1-2):63-77.

Zhang L, Tizard IR. **Activation of a mouse macrophage cell line by acemannan: the major carbohydrate fraction from Aloe vera gel.** Immunopharmacology. 1996 Nov;35(2):119-28.

ABSTRACTS

Djeraba A, Quere P. **In vivo macrophage activation in chickens with Acemannan, a complex carbohydrate extracted from Aloe vera.** Int J Immunopharmacol. 2000 May;22(5):365-72.

Acemannan (ACM 1), a beta-(1,4) -acetylated mannan isolated from Aloe vera, can be used as an effective adjuvant in vaccination against some avian viral diseases. Our results demonstrate a quick and lasting in vivo priming effect of ACM 1 on macrophage response after intramuscular inoculation in chickens (500 microg per 2-month-old bird). In response to IFN-gamma in vitro, monocytes from ACM 1-treated chickens exhibited a strong enhancement of NO production from 3 to 9 days p.i., but a weaker effect on MHC II cell surface antigen expression on day 3 p.i. A stimulating effect of ACM 1 treatment was also observed on spontaneous and inducible NO production for splenocytes only on day 3 p.i. By that time, splenocytes exhibited a strong higher capacity to proliferate in response to the T cell-mitogen PHA. At the same time, the in vivo capacity to produce NO, measured by the (NO(-)(2)+NO(-)(3)) serum level after intravenous LPS injection, increased greatly from 3 to 9 days p.i. In conclusion, ACM 1 was able efficiently and durably to increase the activation capacity of macrophages from the systemic immune compartment (in particular from the blood and spleen after an intramuscular injection) in chickens, especially for NO production. These findings provide a better understanding of the adjuvant activity of ACM 1 for viral and tumoral diseases.

Harris C, Pierce K, King G, Yates KM, Hall J, Tizard I. **Efficacy of acemannan in treatment of canine and feline spontaneous neoplasms.** Mol Biother. 1991 Dec;3(4):207-13.

Forty-three dogs and cats with spontaneous tumors were treated with the immunostimulating polysaccharide acemannan by

intraperitoneal and intralesional routes of administration. Tumors from 26 of these animals showed histopathological evidence of immunological attack as shown by marked necrosis or lymphocytic infiltration. Thirteen showed moderate to marked tumor necrosis or liquefaction. Twenty-one demonstrated lymphoid infiltration, and seven demonstrated encapsulation. Twelve animals showed obvious clinical improvement as assessed by tumor shrinkage, tumor necrosis, or prolonged survival; these included five of seven animals with fibrosarcomas. It is believed that acemannan exerts its antitumor activity through macrophage activation and the release of tumor necrosis factor, interleukin-1, and interferon.

Lee JK, Lee MK, Yun YP, Kim Y, Kim JS, Kim YS, Kim K, Han SS, Lee CK. **Acemannan purified from Aloe vera induces phenotypic and functional maturation of immature dendritic cells.** *Int Immunopharmacol.* 2001 Jul;1(7):1275-84.

Acemannan, a major carbohydrate fraction of Aloe vera gel, has been known to have antiviral and antitumoral activities in vivo through activation of immune responses. The present study was set out to define the immunomodulatory activity of acemannan on dendritic cells (DCs), which are the most important accessory cells for the initiation of primary immune responses. Immature DCs were generated from mouse bone marrow (BM) cells by culturing in a medium supplemented with GM-CSF and IL-4, and then stimulated with acemannan, sulfated acemannan, and LPS, respectively. The resultant DCs were examined for phenotypic and functional properties. Phenotypic analysis for the expression of class II MHC molecules and major co-stimulatory molecules such as B7-1, B7-2, CD40 and CD54 confirmed that acemannan could induce maturation of immature DCs. Functional maturation of immature DCs was supported by increased allogeneic mixed lymphocyte reaction (MLR) and IL-12 production. The differentiation-inducing activity of acemannan was almost completely abolished by chemical sulfation. Based on these results, we propose that the adjuvant activity of acemannan is at least in part due to its capacity to promote differentiation of immature DCs.

Montaner JS, Gill J, Singer J, Raboud J, Arseneau R, McLean BD, Schechter MT, Ruedy J. **Double-blind placebo-controlled pilot trial of acemannan in advanced human immunodeficiency virus disease.** *J Acquir Immune Defic Syndr Hum Retrovirol.* 1996 Jun 1;12(2):153-7.

SUMMARY: We assessed the safety and surrogate markers' effect of acemannan as an adjunctive to antiretroviral therapy among patients with advanced HIV disease receiving zidovudine (ZDV) or didanosine (ddI) in a randomized, double-blind, placebo-controlled trial of acemannan (400 mg orally four times daily). Eligible patients of either sex had CD4 counts of 50-300/microl twice within 1 month of study entry and had received 26 months of antiretroviral treatment (ZDV or ddI) at a stable dose for the month before entry. CD4 counts were made every 4 weeks for 48 weeks. P24 antigen was measured at entry and every 12 weeks thereafter. Sequential quantitative lymphocyte cultures for HIV and ZDV pharmacokinetics were performed in a subset of patients. Sixty-three patients were randomized. All were males (mean age 39 years). The mean baseline CD4 counts were 165 and 147/microl in the placebo and acemannan groups, respectively; 90 percent of the patients were receiving ZDV at entry. Six patients in the acemannan group and five in the placebo group developed AIDS-defining illnesses. There was no statistically significant difference between the groups at 48 weeks with regard to the absolute change or rate of decline at CD4 count. Among ZDV-treated patients, the median rates of CD4 change (ACD4) in the initial 16 weeks were - 121 and - 120 cells per year in the placebo and acemannan groups, respectively ($p = 0.45$), ACD4 from week 16 to 48 was 0 and - 61 cells per year in the acemannan and placebo groups ($p = .11$), respectively. There was no statistical difference between groups with regard to adverse events, p24 antigen, quantitative virology, or pharmacokinetics. Twenty-four patients, 11 receiving placebo and 13 receiving acemannan, discontinued study therapy prematurely, none due to serious adverse reactions. Our results demonstrate that acemannan at an oral daily dose of 1600 mg does not prevent the decline in CD4 count characteristic of progressive HIV disease. Acemannan showed no significant effect on p24 antigen and quantitative virology. Acemannan was well tolerated and showed no significant pharmacokinetic interaction with ZDV.

Pugh N, Ross SA, EISOhly MA, Pasco DS. **Characterization of Aloeride, a new high-molecular-weight polysaccharide from Aloe vera with potent immunostimulatory activity.** *J Agric Food Chem.* 2001 Feb;49(2):1030-4.

We have characterized a new immunostimulatory polysaccharide called Aloeride from commercial aloe vera (*Aloe barbadensis*) juice. Aloeride is between 4 and 7 million Da, and its glycosyl components include glucose (37.2%), galactose (23.9%), mannose (19.5%), and arabinose (10.3%). At 0.5 microg/mL Aloeride increased NF-kappa B directed luciferase expression in THP-1 human monocytic cells to levels 50% of those achieved by maximal concentrations (10 microg/mL) of LPS. Aloeride induced the expression of the mRNAs encoding IL-1beta and TNF-alpha to levels equal to those observed in cells maximally activated by LPS. Acemannan, the major carbohydrate component from aloe, used at 200 microg/mL in the macrophage assay resulted in negligible NF-kappa B activation. Analysis of acemannan and Aloeride using size-exclusion chromatography suggests that the low activity of acemannan is due to trace amounts of Aloeride. Although Aloeride comprises only 0.015% of the aloe juice dry weight, its potency for macrophage activation accounts fully for the activity of the crude juice.

Stuart RW, Lefkowitz DL, Lincoln JA, Howard K, Gelderman MP, Lefkowitz SS. **Upregulation of phagocytosis and candidicidal activity of macrophages exposed to the immunostimulant acemannan.** *Int J Immunopharmacol.* 1997 Feb;19(2):75-82.

Previous studies by these investigators have shown that mannosylated bovine serum albumin (m-BSA) enhances the respiratory burst (RB), phagocytosis, and killing of *Candida albicans* by resident murine peritoneal macrophages (MO). Upregulation of the above MO functions was associated with binding of m-BSA to the MO-mannose receptor. The present study was done to determine if the immunostimulant, acemannan prepared from aloe vera, could stimulate MO in a similar manner. Resident peritoneal MO collected from C57BL/6 mice were exposed to acemannan for 10 min. The RB was measured using chemiluminescence and demonstrated approximately a two-fold increase above the media controls. In studies involving phagocytosis, MO were exposed to acemannan, washed and exposed to *Candida* at a ratio of 1:5. The percent phagocytosis and *Candida* killing were determined using fluorescence microscopy. There was a marked increase in phagocytosis in the treated cultures (45%) compared to controls (25%). Macrophages exposed to acemannan for 10 min resulted in ca 38% killing of *Candida albicans* compared with 0-5% killing in controls. If MO were incubated with acemannan for 60 min, 98% of the yeast were killed compared to 0-5% in the controls. The results of the present study indicate that short term exposure of MO to acemannan upregulates the RB, phagocytosis and candidicidal activity. Further studies are needed to clarify the potential use of this immunostimulant as an anti-fungal agent.

Ramamoorthy L, Tizard IR. **Induction of apoptosis in a macrophage cell line RAW 264.7 by acemannan, a beta-(1,4)-acetylated mannan.** *Mol Pharmacol.* 1998 Mar;53(3):415-21

Acemannan is a polydispersed beta-(1,4)-linked acetylated mannan with antiviral properties. It is an immunomodulator, and studies in our laboratory have shown that it causes activation of macrophages. In the presence of IFN γ , acemannan induced apoptosis in RAW 264.7 cells. These cells exhibited chromatin condensation, DNA fragmentation, and laddering characteristic of apoptosis. The induction of apoptosis by acemannan and IFN γ does not seem to be mediated by nitric oxide, since N-nitro-L-arginine methyl ester, the nitric oxide inhibitor, had no effect. Acemannan in the presence of IFN γ also inhibited the expression of bcl-2. These results suggest that acemannan in the presence of IFN γ induces apoptosis in RAW 264.7 cells through a mechanism involving the inhibition of bcl-2 expression.

Usinger WR. **A comparison of antibody responses to veterinary vaccine antigens potentiated by different adjuvants.** *Vaccine.* 1997 Dec;15(17-18):1902-7.

Six adjuvant formulations were compared for their ability to potentiate the primary and memory antibody responses in mice to three companion animal vaccine immunogens--feline leukemia virus (FeLV), feline immunodeficiency virus (FIV), and a recombinantly-derived heartworm antigen. The combination of a novel bacterial immunostimulator, gliding bacterial adjuvant (GBA), either adsorbed onto an aluminum hydroxide gel (Rehydragel HPA), or emulsified with a vehicle of polyalcohol and detergent, elicited the strongest memory responses to both virus preparations. Both forms of aluminum hydroxide gels administered without GBA gave similar levels of adjuvant effects, on par with or greater than those generated by incomplete Freund's adjuvant (IFA). The Acemannan immunostimulant was not effective in increasing the responses to the virus antigens, but increased the primary response to the heart-worm antigen over tenfold from control levels. All preparations appeared to be well tolerated, with no detectable adverse reactions observed in any of the 250 mice used. The proven safety of aluminum hydroxide adjuvants and the apparent absence of adverse reactions seen with GBA make this vehicle/adjuvant formulation worthy of additional study.

Womble D, Helderman JH. **The impact of acemannan on the generation and function of cytotoxic T-lymphocytes.** *Immunopharmacol Immunotoxicol.* 1992;14(1-2):63-77.

Acemannan, an antiviral agent with immune enhancement capabilities, was studied for its impact on cytotoxic T-lymphocyte (Tc) function generated in response to alloantigen. To investigate whether acemannan directly stimulated the generation of Tc from primary mixed lymphocyte cultures (MLC), the drug was added at the initiation of the MLC. There was a dose-related, statistical increase in killer T-cell generation produced by acemannan in the clinically relevant dose range. The lowest test dose of the drug (2.6×10^{-9} M) increased chromium release nearly two-fold; the 2.6×10^{-8} M dose gave a maximal 3.5 fold increase in cytotoxic T-cells. To study whether acemannan enhanced the capacity of Tc once generated to alloantigen to destroy targets bearing the sensitizing antigens, MLR were established in the absence of any drug. Acemannan at the two highest doses increased the functional capacity of Tc to destroy target cells to which they had been sensitized in the MLR. To control for the possibility that acemannan was directly cytotoxic to target cells, targets were incubated alone with drug and without sensitized killer T-cells. No dose of acemannan was found to be cytotoxic to these cells. In conclusion, acemannan did enhance the generation of cytotoxic T-cells when added at the initiation of the MLR. When acemannan was added at the completion of allostimulation, an increase of almost 50% killing by Tc was also observed. These effects can not be explained by direct drug related toxicity and suggest a functional correlate to the previously described immune enhancing properties of the agent. As this drug is being tested for the treatment of HIV infections, these data provide at least one immunologic mechanism by which acemannan may be clinically salutary.