

HIV infection and OTC supplements: do they really have an impact?



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This article deals with immunologically active nutritional supplements in HIV-infected patients: the science, the effects and recommendations.

With the numbers of persons living with HIV disease increasing at alarming rates and the debate over access to antiretroviral drugs (ARTs) still raging, it is evident that most patients will try to manage themselves (self medicate) or will approach their medical practitioners for advice. A great number of 'fad' products can be found on the shelves of health food stores or pharmacies, and it is important to know what has been clinically tested in HIV disease and what products should be avoided. The general practitioner needs to know what scientific basis exists for the recommendation for usage of such products.

A study conducted in the Boston area (USA) found that 68% of 180 HIV-positive patients interviewed reported the use of herbs, vitamins or dietary supplements in conjunction with conventional drugs specific for HIV. In another report, 39% of 657 Canadian patients from British Columbia reported using complementary and alternative modalities (CAMs) but this tended to be restricted to young and highly educated individuals. There is no doubt then that in developed countries, patients have recourse to CAM despite the availability of ARTs. We can therefore expect that because the price of ARTs has decreased in South Africa, the demand by patients will increase. It is also important to recognise that clinicians may not be adequately informed on the use of CAM in HIV disease, since the 'alternative' medical approach is not part of the medical curriculum at most medical faculties.

In order to provide some guidelines to clinicians, this report examines the use of CAM therapies reported to have immune modulating activities. These are limited mainly to the herbal extracts or dietary supplements known to have such properties. It does not include however the potential use of other modalities such as reflexology, psycho-neuro-immunology (PNI), aromatherapy, etc., all of which have been shown to have important beneficial roles in the management of HIV disease.

VITAMINS AND OTHER DIETARY SUPPLEMENTS

It has been demonstrated that micronutrient supplementation may be an important prophylactic and therapeutic measure for HIV-1 infected patients and is possibly one of the few potential interventions for low-income countries. For instance, poor maternal micronutrient status has been shown to be associated with faster clinical and immunological progression of HIV-1 disease and with adverse birth outcomes, including fetal retardation and death. In recent years, many groups have investigated the outcome of HIV infection in patients supplemented with vitamin B or multivitamins, including/excluding vitamin A in pregnancy. Some studies have shown that high doses of vitamin B₆ supplements were associated with improved survival of patients while zinc supplementation was associated with poorer survival.

Since specific micronutrient abnormalities occur in HIV disease, low plasma or

serum levels of many of these (mostly vitamins A, B₆, B₁₂ and zinc) have been associated with poor outcomes. In dietary uptake studies, it has been shown that increased intake of iron, niacin, riboflavin and vitamins A and E is associated with decreased progression to AIDS.¹ Finally, in small preliminary clinical trials, - carotene given to infected individuals has been shown to increase natural killer cell markers, white blood cell numbers, percentage change in CD4+ counts and CD4:CD8 ratios. It should be remembered that owing to possible teratogenic effects of high doses of vitamin A in pregnancy, the International Vitamin A Consultative Group has advised that an upper limit of 10 000 IU/day should not be exceeded. There is no doubt that antioxidants (such as vitamins C and E) or reduced glutathione or n-acetyl cysteine are also important for the management of HIV disease since most patients are under oxidative stress and the viral replication cycle is enhanced due to increased levels of oxidants. Therefore, the use of antioxidant preparations is advisable.

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HERBAL IMMUNE MODULATORS

Many herbs have been used through the ages in an attempt to boost the immune response to infectious agents as well as in can-

cer. The most common of these are discussed below.

Echinacea

Echinacea purpurea (Fig. 1), *E. angustifolia* and *E. pallida* were the most popular herbs used by Native Americans and today we see many such products on the shelves of pharmacies or health food stores. The *in vitro* testing of extracts of either the leaves or flowers of such herbs (especially the polysaccharides) has shown these to increase the production of tumour necrosis factor-alpha (TNF- α). The hesitation in using such products in HIV disease comes from the observation that most infected patients present with raised plasma levels of TNF- α and it is believed that this pro-inflammatory factor contributes to the pathogenesis of HIV-related disease symptoms (weight loss, chronic pain, etc.). However, it is argued that the large polysaccharides are poorly absorbed when orally ingested and that those tested in the test tube were culture-derived and not the same as those present in the natural plant extract.



Fig. 1. Flower of *Echinacea purpurea*.

There is some scientific literature that shows that when cells obtained from HIV-positive patients are incubated with *Echinacea* extracts, an enhanced cellular activity can be detected.² Since these activities are abnormal in people living with HIV, it can be argued that the use of such extracts would translate into clinical bene-

fit. However, a trial to prove or disprove the benefit of this herb in HIV disease is lacking. We have seen some preliminary study results, despite the contraindication of using it as listed in the German Commission E monograph on *Echinacea*. It still remains controversial and we await further clinical trials before any final recommendations can be made.

European mistletoe

Viscum album has been used since ancient times for a variety of ailments. This parasite seen growing on oak trees (Fig. 2) was long considered a sacred symbol and potent medicine by the Druids. Similarly to the *in vitro* activities for *Echinacea*, mistletoe extracts have been shown to enhance the production of TNF- α by leucocytes but unlike *Echinacea*, administration of the *Viscum album* extract to humans intravenously or orally leads to raised plasma levels of the TNF- α . Hence the contraindication to the use of this herb in HIV disease. On the other hand, some studies have provided some justification for its use in HIV disease: aqueous extract of mistletoe inhibits reverse transcription *in vitro*.



Fig. 2. The branches and berries of the mistletoe (*Viscum album*).

Despite the abovementioned reservations with regard to the use of mistletoe in HIV disease, some studies have yielded positive results: a study reported on its subcutaneous application in 12 individuals and subsequently in a larg-

er cohort of patients in a dose escalation study. Patients were reported to display stable CD4 cell counts or increases of 20% or more in the CD4+ lymphocyte levels after 12 weeks of therapy.³ Further studies are necessary to determine whether *Viscum album* extract should be used as an adjunct to ARTs or other natural therapies.

Licorice

Two of the most studied botanicals with immune modulatory activities are the European *Glycyrrhiza glabra* (licorice) and its close Asian relative *Glycyrrhiza uralensis* (gancao). The main glycoside from licorice, glycyrrhizin, appears to have anti-viral and immune-modulating properties. Since 1980, intravenous glycyrrhizin has been used in Japan to treat patients infected with HIV and it was found to be effective for suppressing levels of HIV.⁴ However, this is not the optimal approach to treating HIV patients, given its inconvenience and expense of the intravenous injection. Three long-term studies have shown that oral administration of glycyrrhizin is effective in suppressing the viral replication and maintaining immune function in patients. Although uncontrolled, the results seem impressive: none of the ten patients receiving the glycyrrhizin deteriorated during the study while a group of patients not on the study showed progression of the disease.

The dose of glycyrrhizin used was 150 - 225 mg per day in divided doses — at these doses the pseudoaldosteronism syndrome may develop in some patients. Because glycyrrhizin suppresses cortisol catabolism by the kidneys and liver, it may lead to increases in the serum levels of cortisol and resultant increased potassium excretion by the kidneys. If not checked, hypertension, oedema and related weight gain or even

more serious problems may develop. These risks may be reduced or prevented by advising patients to follow diets high in fruits and vegetables or by administering potassium concomitantly.

The results obtained from the use of licorice are most exciting but further larger studies are required in order to confirm the preliminary observations. In some circles, it is advocated that since *Glycyrrhiza* has many other beneficial constituents, it would be best to use the whole plant extract rather than the purified glycyrrhizin. Furthermore, a deglycyrrhized licorice preparation would be useful for the management of aphthous stomatitis (or even peptic ulcers) but this would not have much effect on the HIV infection itself.

Other herbals with immune modulating properties

Most of the other herbals heralded for use in HIV infection are very preliminary in status. The use of the root and rhizome of the Siberian ginseng (*Eleutherococcus senticosus*) has been studied in few patients and reported to have caused profound increases in CD4+ cells after oral ingestion of the extract.⁵ However, further studies have not been forthcoming.

Another botanical used is the Reishi mushroom extract (*Ganoderma lucidum*). This has been used for centuries in Asia as an immune modulator for patients diagnosed with cancer and preliminary data have shown that the reishi extract enhances the activities of the CD4 cells prepared from HIV-infected patients. Several compounds with anti-HIV activity *in vitro* (especially anti-proteases) have been identified from the extract of this mushroom.⁶ However, despite these promising preliminary data, no clinical trial seems to have been conducted.

The plant sterols/sterolins

A mixture of sterols and sterolins has been researched in the last 12 years as an alternative management approach to our local infected population. This mixture was used in HIV disease after scientific proof that it had immune modulatory activities on the T_{H1} CD4 cells.

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Patients on the supplement containing a patented mixture of the plant sterols/sterolins have shown stable CD4 cell numbers over a follow-up period of 40 months, during which time their viral loads declined significantly. This is especially true in the group of patients who started the study with intact immune systems (CD4 cell numbers above 500/ μ l blood). These patients displayed the most promising effects of this supplement. Interestingly, in this group of patients, 15% became viral load undetectable within a period of 12 months after initiation of the study.⁷

Furthermore, a cross-sectional study of patients on the supplement compared with those not on the supplement but with similar CD4 cell numbers showed that the sterol/sterolin supplemented patients had better cytokine secretion patterns. This study indicated that those patients on the sterols/sterolins had a beneficial T_{H1} CD4 phenotype: this translates

into better cellular responses to the virus or virally infected host cells.⁸

For too long the immune system has remained the orphan in this disease and it is time to include such management strategies since the use of such therapies could prevent many of the severe deficiencies and immune dysfunction.

Sterols/sterolins versus Hypoxis plant (African potato) extract? This is a decision that many infected patients face. Our initial study was conducted on the *Hypoxis* plant extract but was discontinued due to the demonstration of bone marrow suppression in several patients with terminal cancer. The total plant extract contains molecules with unknown chemical structures at present and these may have long-term detrimental effects. Furthermore, many case reports from KwaZulu-Natal have emerged concerning the admittance to the emergency services of patients who had ingested concoctions derived from this plant and yet many such preparations are freely available from street vendors.

IMMUNE MODULATION: GOOD OR BAD?

We are aware of several new studies evaluating the use of other molecules with immune-modulating properties in HIV disease. For

instance, new studies are evaluating the use of recombinant cytokines, hormone precursors, antioxidants and even thalidomide. The impact of these on the immune response of HIV-infected individuals seems promising as adjuvants in the management of infected patients.

For too long the immune system has remained the orphan in this disease and it is time to include such management strategies since the use of such therapies could prevent many of the severe deficiencies and immune dysfunction. We should never contemplate that such approaches could ever replace the use of antiretroviral regimens. However, modulation of an effective immunity to the virus itself has a major role to play in this infection. After all, it is the loss of effective immunity that allows disease progression.

References available on request.

IN A NUTSHELL

Many HIV-infected patients have recourse to alternative therapies freely available on the market.

Although marketed as immunity-enhancing herbs, not all have been clinically tested specifically in HIV disease.

Some therapies should be used with reservation: those which can promote inflammation should be avoided in HIV disease.

Due to the numerous micro-nutrient deficiencies which develop in HIV patients, balanced multivitamin intake should be encouraged.

Many complementary therapies can be used in conjunction with registered ARVs: the practitioner should be informed of their usage.

SINGLE SUTURE

Blood pressure and cognitive impairment in heart failure patients

In an Italian study published in *Neurology* (2001; 57: 1986-1992), cognitive impairment was found significantly more frequently among patients with heart failure than among those without heart failure (26% v. 19%). In analyses adjusted for several confounding variables, cognitive dysfunction was associated with lower systolic blood pressure (BP) among heart failure patients: systolic BP lower than 130 mmHg was found in 46% of heart failure patients with cognitive impairment and in 27% of those without impairment — a significant difference. Among patients without heart failure, there was no correlation between BP and cognitive dysfunction.

Allan S Brett, MD, writing in *Journal Watch* (8 January 2002), comments, ‘Undoubtedly there are other confounding variables that were not accounted for in this study, and causal links between heart failure, cognition, and BP remain unclear. Because hypotensive drugs are a mainstay of heart failure therapy, we will face a dilemma if additional research shows that active lowering of systolic BP to below 130 mmHg increases risk for cognitive dysfunction among heart failure patients.’