

See discussions, stats, and author profiles for this publication at: <https://www.researchgate.net/publication/12914684>

# Plant sterols and sterolins: A review of their immune-modulating properties

Article in Alternative medicine review: a journal of clinical therapeutic · July 1999

Source: PubMed

---

CITATIONS

129

READS

1,293

---

2 authors, including:



Patrick Bouic

66 PUBLICATIONS 1,804 CITATIONS

[SEE PROFILE](#)

Some of the authors of this publication are also working on these related projects:



Capacity building in medicines development in South Africa [View project](#)

# Plant Sterols and Sterolins: A Review of Their Immune-Modulating Properties

Patrick J.D. Bouic, PhD and Johan H. Lamprecht, MD

## Abstract

Beta-sitosterol (BSS) and its glycoside (BSSG) are sterol molecules which are synthesized by plants. When humans eat plant foods phytosterols are ingested, and are found in the serum and tissues of healthy individuals, but at concentrations orders of magnitude lower than endogenous cholesterol. Epidemiological studies have correlated a reduced risk of numerous diseases with a diet high in fruits and vegetables, and have concluded that specific molecules, including b-carotene, tocopherols, vitamin C, and flavonoids, confer some of this protective benefit. However, these epidemiologic studies have not examined the potential effect that phytosterols ingested with fruits and vegetables might have on disease risk reduction. In animals, BSS and BSSG have been shown to exhibit anti-inflammatory, anti-neoplastic, anti-pyretic, and immune-modulating activity. A proprietary BSS:BSSG mixture has demonstrated promising results in a number of studies, including *in vitro* studies, animal models, and human clinical trials. This phytosterol complex seems to target specific T-helper lymphocytes, the  $T_H1$  and  $T_H2$  cells, helping normalize their functioning and resulting in improved T-lymphocyte and natural killer cell activity. A dampening effect on overactive antibody responses has also been seen, as well as normalization of the DHEA:cortisol ratio. The re-establishment of these immune parameters may be of help in numerous disease processes relating to chronic immune-mediated abnormalities, including chronic viral infections, tuberculosis, rheumatoid arthritis, allergies, cancer, and auto-immune diseases.

(Altern Med Rev 1999;4(3):170-177)

## Introduction

Beta-sitosterol (BSS) is the major phytosterol in higher plants, and is found in the serum and tissues of healthy individuals at concentrations 800-1000 times lower than that of endogenous cholesterol. Its glycoside,  $\beta$ -sitosterol glycoside (BSSG), is also present in serum in even lower concentrations.<sup>1</sup> These molecules are synthesized in plants; whereas animals obtain them through diet. Many epidemiological studies of groups consuming diets rich in vegetables and fruits have indicated a reduced incidence of various types of cancer, cardiovascular disease, diabetes, and other chronic diseases.<sup>2</sup> Many of these studies have concentrated on the protective effects of well-characterized molecules such as b-carotene, tocopherols, vitamin C, and flavonoids.

P.J.D. Bouic, Ph.D and Johan H. Lamprecht, M.D. - Departments of Medical Microbiology and Pharmacology, Medical Faculty, University of Stellenbosch.

Correspondence address: P.O. Box 19063, Tygerberg 7505, South Africa. E-mail: pjdb@gerga.sun.ac.za

However, such studies have ignored the relative importance of fats in the plants consumed.

The scientific literature is replete with reports of the biological activities of sterols or their glycosides in various animal models. For instance, BSS and its glycoside have been shown to reduce carcinogen-induced cancer of the colon in rats,<sup>3</sup> as well as exhibiting anti-inflammatory,<sup>4</sup> anti-pyretic,<sup>5</sup> anti-complement activity,<sup>6</sup> and insulin-releasing effects.<sup>7</sup>

A proprietary mixture of BSS and BSSG (BSS:BSSG) was studied and found to have profound immune modulating activities. Initial *in vitro* studies were followed by clinical trials in patients with chronic infectious diseases (tuberculosis, HIV, Human Papilloma Virus [HPV]) and non-infectious conditions, such as allergies and rheumatoid arthritis. The trials confirmed the importance of BSS:BSSG in the management of such conditions.

## The Functioning of the Immune System

The immune system is an intricate network of cells and soluble factors released by these cells. B-lymphocytes produce antibodies in response to antigenic stimulation. T-lymphocytes induce either a humoral or cellular response depending on the subset of T cells that are primed upon initial contact with the antigen.<sup>8</sup>

T cells are made up of two distinct subsets, the CD4 helper cell and the CD8 cytotoxic/suppressor cells. Within the CD4 subset there are two types of helper cells. One is the T<sub>H</sub>1-type, which releases interleukin-2 (IL-2) and gamma interferon (IFN- $\gamma$ ). These cytokines bind to and activate the CD8 cytotoxic cells to become effective killers. This type of cellular response is vital to clearing the host of pathogens

which use the intracellular milieu to survive attack by the immune response. Should this cellular response fail, the infection becomes chronic. The second type of helper cell is the T<sub>H</sub>2-type, which secretes IL-4, IL-6, and IL-10, cytokines which are involved in B-lymphocyte differentiation (Table 1). The antibody response is capable of limiting the damage induced by most extracellular organisms.

In health, there is a delicate balance maintained between the activity of T<sub>H</sub>1 and T<sub>H</sub>2 helper cells in that the activity of T<sub>H</sub>1 cells is directly cross-regulated by the T<sub>H</sub>2 cells, and vice versa. However, under certain pathological conditions, especially chronic viral and bacterial diseases, the functioning of T<sub>H</sub>1 cells may be superseded by that of the T<sub>H</sub>2 cells leading to a humoral immune response (antibody production) at the expense of the more protective cellular response. A similar imbalance exists in other chronic conditions, such as allergies and autoimmune disorders. Maintaining the delicate balance between T<sub>H</sub>1 and T<sub>H</sub>2 cells is vital. Many researchers are currently attempting to enhance the activity of T<sub>H</sub>1 helper cells in order to eradicate latent and chronic pathogens.

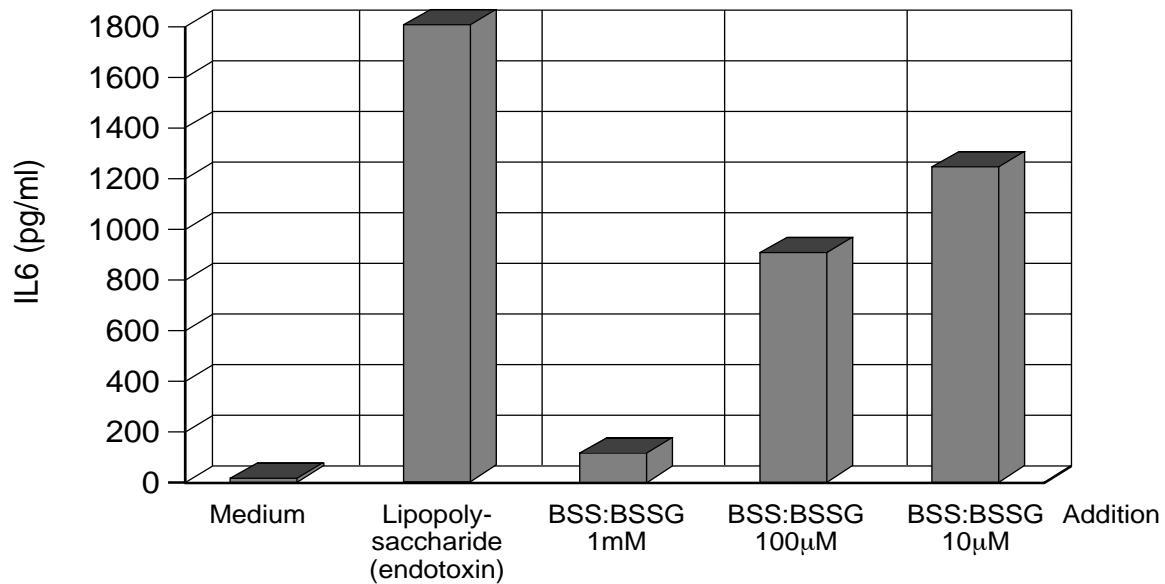
## BSS and BSSG as Immune Modulators

Initial observations using human peripheral blood lymphocytes showed a mixture

**Table 1.** The dichotomy of T helper cells based on their defining cytokine profiles and functions

Cell	Cytokine profile	Function of TH subset
T <sub>H</sub> 1	IFN- $\gamma$ , IL2	Activation of cytotoxic cells Antagonism of T <sub>H</sub> 2 cells
T <sub>H</sub> 2	IL4, IL6, IL10, IL5	Activation and maturation of B cells Antagonism of T <sub>H</sub> 1 cells

**Figure 1.** IL6 Secretion *in vitro*.



of BSS:BSSG in a ratio of 100:1 could influence the cellular proliferation of T-lymphocytes when these were activated by mitogens *in vitro*. The *in vitro* results were confirmed in a small pilot study in which volunteers took a BSS:BSSG complex orally. The *ex vivo* testing of lymphocyte proliferation showed a greatly enhanced response to mitogens. In parallel the lytic ability of the natural killer cells (NK cells) to a cancer cell line *in vitro* was greatly increased in the presence of the BSS:BSSG mixture.<sup>9</sup>

When the profile of cytokine secretion by activated T cells was measured it was discovered that the BSS:BSSG mixture was selective in the above-mentioned activities. Lymphokines belonging to T<sub>H</sub>1-type helper cells were increased, whereas those associated with T<sub>H</sub>2-type helper cells were inhibited or remained unchanged. The BSS:BSSG mixture enhanced the secretion of IL-2 and IFN- $\gamma$ , but inhibited the secretion of IL-4.<sup>10</sup> The specificity toward certain T-helper cells indicates BSS:BSSG could have important regulatory and modulatory activities in diseases where

enhancement of the T<sub>H</sub>1-type helper cells is vital for the effective clearance of particular pathogens. Furthermore, since these plant constituents are able to switch off the secretion of IL-4 in conditions where an overt T<sub>H</sub>2 response predominates, these natural substances should reinstate balance in conditions such as allergies and auto-immune diseases.

Further *in vitro* testing of physiological concentrations of BSS:BSSG on monocyte activity revealed anti-inflammatory properties, via inhibition of both IL-6 and tumor necrosis factor alpha (TNF- $\alpha$ ), in a dose-dependent manner (Figure 1). Diseases characterized by elevated levels of TNF- $\alpha$  and IL-6, which induce tissue damage, include rheumatoid arthritis and systemic lupus erythematosus (SLE).

### **BSS:BSSG as an Adjuvant in the Treatment of Patients with Pulmonary Tuberculosis**

A clinical study of BSS:BSSG complex examined its effect in culture-proven pulmonary tuberculosis (PTB). This was a

blinded, randomized, placebo-controlled trial in drug-sensitive PTB. Patients were hospitalized for the duration of treatment, and sputum culture positivity, chest radiography, weight gain, Mantoux test response, routine hematology, and liver function were evaluated at monthly intervals. Forty-seven patients were enrolled in the six-month study, and all patients were treated with the standard anti-tuberculous regimen of isoniazid, rifampicin and pyrazinamide. No significant differences existed between the variables of each group evaluated at the time of entry into the study.

Sputum conversion in the patient groups were very similar; by the end of the first month of therapy, 58 percent in the treatment group and 61 percent in the placebo group were still sputum culture positive. By the end of the second month, 11 percent of the patients in each group were still positive, but thereafter, no patients had positive sputum cultures. An independent physician and radiologist evaluated the radiological changes seen on the chest radiographs. Although improvement seemed to occur faster in the sterol treated group when compared to their placebo counterparts, the differences were difficult to quantify. Therefore, this parameter was not included in the final analysis of the data.

The most significant differences observed between the groups were in the hematological parameters, including higher lymphocyte ( $p=0.0001$ ), eosinophil ( $p=0.0001$ ), and monocyte counts in the BSS:BSSG group. The placebo group showed higher sedimentation rates when compared to the study group ( $p=0.0001$ ). Possibly the most remarkable difference between the

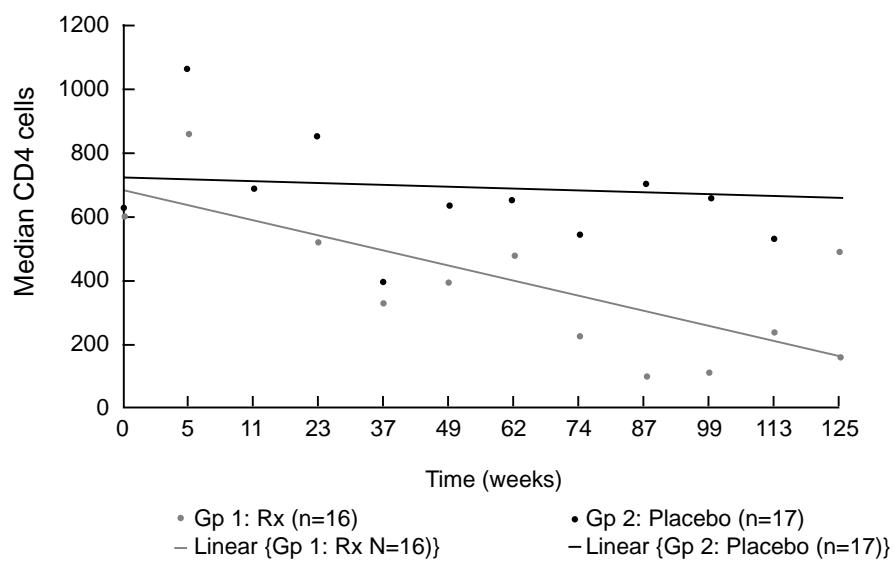
two groups was the difference in weight gain over the six-month period, with the sterol-treated group demonstrating a faster and more pronounced weight recovery.<sup>11</sup>

This was the first study to find a beneficial effect of BSS:BSSG complex in PTB patients. Although the study was small, the statistically significant differences observed between the patient groups suggest further analysis of the immune modulatory activities of BSS:BSSG in multi-drug resistant tuberculosis.

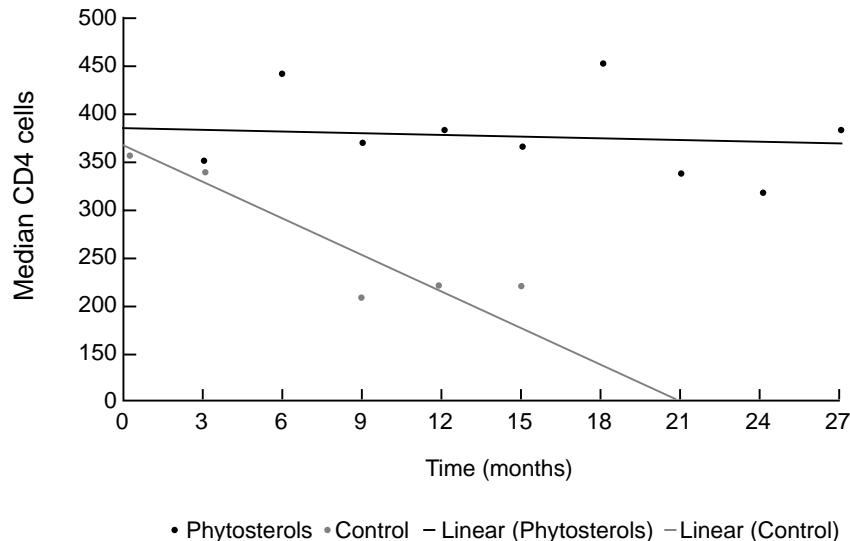
### BSS:BSSG Complex in Felines: A Model of HIV

Domestic cats infected with the retrovirus FIV (considered equivalent to HIV because it induces the same pathogenic mechanisms of CD4 cell loss and opportunistic infections) were examined. Infected cats typically succumb to the infection due to immunosuppression. A group of 33 infected cats was divided into a treatment group (n=16)

**Figure 2.** FIV Pilot Study number 2.



**Figure 3.** HIV Clinical trial (phytosterols vs. control).



or a placebo group ( $n=17$ ).<sup>12</sup> Linear regression of the median CD4 cell numbers of the two groups revealed that the treated group maintained stable immune cell numbers over a period of 168 weeks, whereas those who received the placebo capsules showed disease progression with the typical CD4 cell loss over the same period of time (Figure 2). The end point of such a model is the analysis of mortality in both groups of cats. At present, cats treated with BSS:BSSG complex have exhibited 20 percent mortality compared to 75 percent in the non-treated group.

### Use of BSS:BSSG for Management of HIV Infected Patients

A clinical study (open-labeled trial) is in progress in patients presenting at an infectious disease clinic with a diagnosis of HIV. Pregnant women and children were excluded from the study. Surrogate markers include both the number of CD4 cells (percentages and absolute numbers) as well as other lymphocyte markers, plasma viral loads, and body weight. Basic hematological and chemical parameters are also being monitored. The initial database

consisted of 80 patients who were entered into the trial and followed for 36 months. At the time of this writing over 150 patients are enrolled, with a follow-up period of at least 15 months.

Irrespective of baseline CD4 cell numbers, the median CD4 cell count within the total group of patients has shown relative stability over the analytical period (Figure 3). The data was compared to that obtained from a group of patients attending the same infectious disease clinic but who were not participating in the clinical study. These patients exhibited

the classical decline in CD4 cell numbers. Statistical analysis has found no significant differences between the CD4 counts at entry and at other times during the study in the treated patients, confirming that to date there has been stability in the CD4 counts with no further progression of disease.<sup>12</sup>

Similar positive results were obtained when plasma levels of the pro-inflammatory monokine IL-6 were compared at baseline and again after six months. IL-6 levels decreased significantly, indicating less inflammation, which could explain the CD4 cell stability in these individuals.

Plasma viral loads also gradually declined over time.<sup>12</sup> Sterols and sterolins do not have innate anti-viral properties; the decrease in viral loads is attributable to enhanced activity of the cell-mediated immune response which controls viral replication.

Evaluation of a small participating group found the  $T_H1/T_H2$  profile, after at least 12 months of therapy with BSS:BSSG, was comparable to that observed in healthy HIV-negative controls.<sup>13</sup> In contrast, a group of infected patients not on any therapy exhibited

the typical predominance of  $T_H2$  responses after *in vitro* activation of CD4 cells (Table 2). The ability to maintain a protective  $T_H1$  cellular response has long-term prognostic value, as disease progression is attributed to a failure of this response to control viral replication.<sup>14</sup>

### BSS:BSSG for Preventing Stress-Induced Immune Suppression

Individuals participating in marathon running or other endurance events are prone to bacterial and viral respiratory infections. Research has shown this susceptibility is due to a transient, hormone-induced redistribution in immune cells, as well as a decline in the functionality of the cells.<sup>15</sup>

The potential of BSS: BSSG complex to inhibit immune suppression in a group of volunteers participating in an ultramarathon event was investigated in a double blind, placebo-controlled study. The study found the hematological changes which accompany endurance exercise were more pronounced in individuals who received placebo than in those who received the active capsules. The placebo individuals demonstrated neutrophilia with severe lymphopenia characterized by a profound decrease in the total number of T cells, especially the T helper (CD4 positive) subset. These abnormalities were primarily negated or reversed in volunteers in the treatment group.<sup>16</sup>

Possibly the most dramatic differences between the groups in the study were the changes in serum IL-6 and the cortisol:dehydroepiandrosterone sulfate (DHEAs) ratio. Volunteers in the BSS:BSSG group showed a decline in cortisol, with a parallel increase in serum DHEAs levels, and a

decline in IL-6.<sup>16</sup> Modulation of these hormones has a direct impact on the redistribution of lymphocytes during stress episodes and significantly affects the immune system's ability to respond to potential or ongoing immune challenges. Abnormally high levels of IL-6 (such as is seen in chronic inflammatory conditions) and decreased levels of DHEAs (such as is seen in HIV, SLE, and other autoimmune conditions) characterize many pathological states.

### On-Going Clinical Studies with BSS:BSSG Complex

At present, new clinical studies of the following conditions are being conducted:

- Rheumatoid arthritis: This chronic inflammatory and destructive autoimmune disease is typified by increased levels of IL-6

**Table 2.** The maintenance of  $T_H1$  responses by HIV positive patients receiving Sterinol™: Ratio of  $T_H1$  versus  $T_H2$  CD4+ cells activated *in vitro*.

	7 Hours	18 Hours
Healthy HIV- (n=15)	15.8	9.5
HIV+ BSS:BSSG treated (n=15)	30.7	24.6
HIV+ No treatment (n=15)	5.6	5.0

within the affected joints and an abnormal regulation of immune cells, due to the predominance of  $T_H2$ -type helper cells which promote inflammation and antibody synthesis.<sup>17</sup>

- Cervical lesions induced by the Human Papilloma Virus (as detected by

cytology): Current literature reports such lesions are indicative of an abnormal clearance of the virus and, if left untreated, can lead to carcinoma requiring conization and possibly hysterectomy. Many anecdotal cases of women having used BSS:BSSG complex for this condition have been reported.

- Chronic rhinitis and sinusitis: A small, placebo-controlled study in affected individuals indicates this allergic condition can be controlled by BSS:BSSG complex.

- Hepatitis C virus carrier status: New clinical data from physicians using BSS:BSSG complex report control of liver damage, with a concomitant improvement in liver function and decline of virus within the plasma in these patients.

## Conclusions

The BSS:BSSG complex is a new, natural immune modulator which has demonstrated promising results in a number of clinical trials. These important plant constituents seem to specifically target T-helper cells, and may help to restore balance between  $T_H1$  and  $T_H2$  cells. The end result of this immune modulation is an increase in  $T_H1$ -related cytokines, a decrease in  $T_H2$ -related cytokines, increased lymphocyte proliferation, and greater NK cell activity. The BSS:BSSG complex has also been shown to help normalize the DHEA:cortisol ratio, which can have profound positive results on the immune system. The re-establishment of these immune parameters may be of help in numerous disease processes relating to chronic immune-mediated abnormalities, including chronic viral infections, tuberculosis, rheumatoid arthritis, allergies, cancer, and auto-immune diseases.

Acknowledgements: The authors wish to thank Essential Sterolin Products (Pty) Ltd., of South Africa, the worldwide distributor of Moducare™ Sterinol™ the BSS:BSSG complex used in the clinical studies mentioned above.

## References

1. Pegel KH. The importance of sitosterol and sitosterolin in human and animal nutrition. *SA J Sci* 1997;93:263-268.
2. Dwyer JT. Health aspects of vegetarian diets. *Am J Clin Nutr* 1988;48:712-738.
3. Raicht RF, Cohen BI, Fazzini EP, et al. Protective effect of plant sterol against chemically induced colon tumors in rats. *Cancer Res* 1980;40:403-405.
4. Yamamoto M, Matsui T, Sugiyama K, et al. Anti-inflammatory active constituents of *Aloe arborescens* Miller. *Agric Biol Chem* 1991;55:1627-1629.
5. Gupta MB, Nath R, Srivastava N, et al. Anti-inflammatory and anti-pyretic activities of b-sitosterol. *Planta Med* 1980;39:157-163.
6. Yamada H, Yoshino M, Matsumoto T, et al. Effects of phytosterols on anti-complementary activity. *Chem Pharm Bull* 1987;35:4851-4855.
7. Ivorra MD, D'Ocon MP, Paya M, Villar A. Antihyperglycemic and insulin releasing effects of  $\beta$ -sitosterol 3- $\beta$ -D-glycoside and its aglycone  $\beta$ -sitosterol. *Arch Int Pharmacodyn Ther* 1988;296:224-231.
8. Rook GA, Hernandez-Pando R, Lightman SL. Hormones, peripherally activated prohormones, and the regulation of the TH1/TH2 balance. *Immunol Today* 1994;15:301-303.
9. Bouic PJD, Etsebeth S, Liebenberg RW, et al. Beta-sitosterol and Beta-sitosterol glycoside stimulate human peripheral blood lymphocyte proliferation: implications for their use as an immunomodulatory vitamin combination. *Int J Immunopharmacol* 1996;18:693-700.
10. Myers L, Bouic PJD. Flow cytometric analysis of the TH1-TH2 shift in allergic individuals using Moducare™ (sterols/sterolins). 26<sup>th</sup> Annual Congress of the Physiology Society of Southern Africa; 1998.
11. Donald PR, Lamprecht JH, Freestone M, et al. A randomised placebo-controlled trial of the efficacy of beta-sitosterol and its glycoside as adjuvants in the treatment of pulmonary tuberculosis. *Int J Tuberc Lung Dis* 1997;1:518-522.
12. Bouic PJD. Immunomodulation in HIV/AIDS: the Tygerberg/Stellenbosch University

- experience. *AIDS Bull* 1997;6:18-20.
- 13. Breytenbach U, Bouic PJD. Flow cytometric analysis of the TH1-TH2 balance in healthy individuals and patients infected with the Human Immunodeficiency virus (HIV). 25<sup>th</sup> Annual Congress of the Physiology Society of Southern Africa; 1997.
  - 14. Shearer GM, Clerici M. Cytokine profiles in HIV Type 1 disease and protection. *AIDS Res Hum Retroviruses* 1998;14:S149-S152.
  - 15. Nieman DC. Exercise, infection and immunity. *Int J Sports Med* 1994;15:S131-S141.
  - 16. Bouic PJD, Clark A, Lamprecht J, et al. The effects of b-sitosterol (BSS) and b-sitosterol glycoside (BSSG) mixture on selected immune parameters of marathon runners: inhibition of post marathon immune suppression and inflammation. *Int J Sports Med* 1999;(In Press)
  - 17. Bouic PJD. Sterols/sterolins: the natural, non-toxic immuno-modulators and their role in the control of rheumatoid arthritis. *The Arthritis Trust Newsletter* 1998;Summer:1-4.