Introduction

Beta-sitosterol (BSS) is the major phytosterol in higher plants and is found in the serum and tissues of healthy individuals due to the ingestion of fruits and vegetables. Many epidemiological studies of populations consuming diets rich in vegetables and fruits have indicated a lower incidence of various cancers, cardiovascular disease, diabetes and other chronic diseases of developed countries. Most of such studies have concentrated on well-characterized molecules such as (-carotene, tocopherols, Vitamin C and flavonoids but 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 glucosides in various animal models. For instance, BSS and BSSG have been shown to reduce carcinogen-induced cancer of the colon in a rat model as well as exhibiting anti-inflammatory, anti-pyretic and insulin-releasing properties. We have been studying the immune-modulating activities of these fats for the last 12 years and have applied a proprietary mixture of BSS and BSSG clinically in humans as well as in several animal models. This mixture is commercially available as a supplement called Moducare™.

Functioning of the Immune System

The immune system is an intricate network of lymphoid cells and soluble factors that are released upon challenge. The lymphoid cells are made up of distinct cells, namely B-lymphocytes that make antibodies and T cells which control the immune response. The T cells are made up of 2 subsets, the so-called CD4 T helpers and the CD8, T suppressors/cytotoxic cells. The latter are responsible for the destruction of host cells that have become transformed or infected by intracellular pathogens (viruses, bacteria, etc). The functioning of both the CD8 and B cells are directly under the control of the CD4 helpers due to different cytokines secreted by the T helpers. There are 2 types of helpers: the Th1 CD4 cells secrete the factors IL2 and IFN-γ which activate the CD8 cells in order that the cell-mediated arm of the immune response is activated. On the other hand, the Th2 CD4 cells (secreting IL4, IL6, IL10) are directly responsible for the activation and differentiation of B-lymphocytes into antibody manufacturing factories. In health, there is a delicate balance between the activity of Th1 and Th2 cells in that the activity of one sub-type of CD4 cells is cross-regulated by the activity of the other sub-type (Figure 1). However, in certain pathological conditions, especially chronic viral and bacterial diseases, the functioning of Th2 cells may be superceded by that of the Th1.
cells, leading to a non-protective humoral response at the expense of the cellular response. Similar abnormalities are present in allergic conditions as well as in selected auto-immune processes.

The Sterol/Sterolin Mixture as Immune Modulators

In order to understand the possible impact of one of the major phytosterols, namely BSS, and its glucoside BSSG on human health, it is necessary to consider the in-vitro data and how these could translate into in-vivo benefits.

Initial observations using human lymphocytes indicated that a mixture of these 2 plant fats had profound effects on the functioning of T cells. Indeed, a mixture of BSS:BSSG increased the proliferative response of T cells to mitogens in vitro and enhanced the secretion of important regulatory cytokines such as IL2 and IFN-γ. These observations were confirmed in vivo in volunteers ingesting capsules containing the sterol/sterolin mixture.

In parallel, the lytic/cytotoxic activity of the natural killer cells vis-à-vis a cancer cell line was greatly enhanced when pre-incubated with the BSS/BSSG mixture. This enhanced killing ability was possibly due to the enhanced secretion of interleukin 2 and gamma interferon, both of which are known to promote the cellular activities of natural killer cells.

The mixture also has anti-inflammatory activity: the BSS:BSSG is able to inhibit the secretion of both IL6 and TNF-α, factors which induce inflammation and perpetuate a chronic process. Further investigation of the in vitro activity of the sterols/sterolins showed that these plant molecules target preferentially the T helper cells of the Th1 phenotype, hence their importance in conditions and diseases that are typified by an overt humoral immune response and an under-active cellular response. These include autoimmune conditions, allergic responses, chronic viral and bacterial diseases, cancer, etc.

Human Clinical Studies Undertaken

Due to the fact that the BSS and BSSG mixture showed profound effects in vitro and due to the safety profile of these molecules, it seemed appropriate to investigate the effects under clinical trial situations. The clinical studies undertaken concentrated on the anti-inflammatory properties of BSS and BSSG and the diseases targeted included those in which the balance between the activities of Th1 and Th2 CD4 helper cells needed to be modulated. Such diseases include those described in the literature with overt imbalances between the regulatory T cells, as described below.

Pulmonary Tuberculosis

Since the original published in-vitro study showing the immune-modulatory activity of the Moducare, several clinical studies have been initiated. The first of these examined the adjuvant property of the sterol/sterolin mixture in the treatment of patients with sputum-proven pulmonary tuberculosis. This double blind, randomized, placebo-controlled trial showed significant differences between the groups. The placebo group had higher erythrocyte sedimentation rates, lower lymphocyte counts and other...
hematological parameters, as well as differences in weight gain over the 6-month follow-up period. In general, the phytosterol/glucoside mixture-treated group demonstrated a faster clinical recovery.

Phytosterol and Its Glucoside in Preventing Stress-Induced Immune Suppression

Marathon running or any endurance sport leads to transient immune suppression, possibly due to hormone-induced redistribution of immune cells as well as a decline in the functionality of the cells. Individuals competing in such activities are therefore prone to bacterial and viral infections, especially affecting the upper respiratory tract. A model of immune stress was used to test the potential of the BSS/BSSG mixture in preventing these physiological changes in a group of marathon runners. The study found the haematological changes that accompany endurance exercise were more pronounced in individuals who received placebo capsules, compared with those who received the active compounds. The primary endpoints of the study were the presence of neutrophilia, lymphopenia, inversion of the CD4 to CD8 cells in the peripheral blood, increases in the adrenal hormone cortisol and the resulting decline in the antagonist DHEAs (dihydroepiandrosterone sulphate), as well as increases in the pro-inflammatory cytokine, interleukin 6. All of these parameters were present in the placebo group but were partially reversed or totally abrogated in the treatment group. This study therefore showed that the phytosterol mixture appears to have anti-inflammatory properties in vivo and that it could be used to prevent infectious episodes in endurance sport athletes.

Phytosterol Mixture and Rheumatoid Arthritis

A double blind, placebo-controlled study conducted in patients with active rheumatoid arthritis was recently completed and showed the attenuation of disease activity (criteria according to the American College of Rheumatology). The rationale of this study was that due to the potent anti-inflammatory properties of the phytosterol mixture, patients diagnosed with this chronic inflammatory condition should benefit from such an intervention. Markers of activity included erythrocyte sedimentation rates, tender joint counts, swollen joint counts, clinician’s assessment of disease activity, and so on.

Use of the Phytosterol Mixture in Allergic Rhinitis/Sinusitis Patients

As the phytosterol mixture changes the cytokine profile of T cells to a predominant Th2 type, it would seem applicable to test this mixture in allergic conditions where it is known that a predominant Th2 profile prevails (increased interleukin 4 release and abnormal gamma interferon secretion). This ultimately leads to increased IgE antibody synthesis and allergic symptoms, the hallmark of allergies. A group of 24 atopic individuals (mainly pollen sensitivity) were included in a small pilot study and several laboratory and clinical markers of activity were measured over a 12-week period. Statistically significant changes occurred including less rhinorea, less turbinate hypertrophy, less post-nasal drip symptoms, lower IgE plasma levels and higher Th1-producing cells. Subjective improvements were reported by the patients themselves when an international questionnaire was used to record patient symptoms. Some limited ex-vivo data had previously shown immunological changes occurring in the cytokine profiles of lymphocytes of allergic individuals ingesting Moducare capsules.

Conclusions

The mixture of sterols/sterolins (Moducare™ capsules) represents a new modality in the control and enhancement of the immune system. This natural immune modulator with its non-toxic profile may play an important role in the management of patients with infectious diseases, auto-immune conditions and cancer. One should not forget that many chronic inflammatory conditions are due to a dysregulation of the immune system and that the use of such a health supplement could represent a new class of biological response modifier.

Optimal immune health is vital for the prevention of many chronic conditions. Phytosterols are only part of the total puzzle and the role of other micronutrients and minerals must never be oversimplified. The role played by phytosterols in general health, however, has been underestimated for too long. It is time for us to reconsider these simple plant fats, those that are removed from our natural foods, to present to society more appealing products with longer shelf lives!
References


About the Author

Professor Patrick JD Bouic PhD is Head of Immunology at the Faculty of Health Sciences, University of Stellenbosch and he runs a diagnostic service laboratory within the teaching hospital. In 2003, he formed a biotechnology company based in the faculty: he serves as the Chief Technical Officer of the company which focuses on the rendering of specialized laboratory monitoring for clinical trials being conducted in South Africa. He may be contacted via pbouic@synexagroup.com

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