

MODUCARE® – a Brief History and Mode of Action

Moducare® is a mixture of sitosterol* (BSS) and its glucoside sitosterolin (BSSG) in a 100:1 ratio. This formulation was originally marketed in 1974 in Germany, after its beneficial effect in the treatment of benign prostate hypertrophy (BPH) had been established. Two years later, the same BSS/BSSG mixture was marketed in a product for rheumatoid arthritis.

In 1989, Professor Patrick Bouic and his colleagues at the Medical School of the University of Stellenbosch, Capetown, South Africa discovered that both sitosterol and sitosterolin have an immune modulating effect. Their findings, which were published in the *Int J of Immunopharmacology* 1996, 18, 693-700, eventually resulted in the patented product called Moducare®.

Moducare® taken orally at 3 capsules per day (each capsule contains 20.2 mg sterols/sterolins) restores weakened or reduced T cell activity in a balanced proportion of T_{H1} and T_{H2} cells. This enables the immune system to effectively counteract viral diseases (common cold, hepatitis, HIV, etc.) and various microbial diseases (tuberculosis, etc.). Moducare® also corrects a variety of autoimmune conditions (e.g. rheumatoid arthritis) usually arising from an excess secretion of inflammatory factors. However, Moducare® is not a drug: it does not interfere with any metabolic processes of either the patient or an infecting agent but it is rather a catalyst or messenger initiating a correction of existing immune system imbalances or maintaining adequate existing balances. It thereby helps an individual to maintain good health or fight a disease effectively. The use of Moducare® is ideal in conjunction with drug treatments that tend to disturb the T_{H1}:T_{H2} balance or where a disease results in a T_{H1}:T_{H2} imbalance which a drug cannot correct.

**sitosterol*: This compound is usually described in the literature as β-sitosterol or beta-sitosterol. The chemical name is often shortened to “sterol”.

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Summary of Research

Sterols / Sterolins for the Immune System

Reference: Bouic PJD. Sterols and sterolins: new drugs for the immune system? *Drug Discovery Today* 2002; 7:775–78.

Introduction: Despite the rapid increase of scientific knowledge in immune cells and their various subsets over the last 10 years, the medical and drug management of chronic inflammatory and allergic conditions has not changed in the light of these new discoveries. However, a greater understanding of the immune system and how it is controlled by two unique subsets of CD4 lymphocytes (T_{H1} versus T_{H2}) has led to the re-classification of certain types of disorders into specific categories depending on the ratios of these unique cells. As such, chronic conditions can now be specifically targeted through restoration of the T_{H1}:T_{H2} balance.

Plant sterols: new therapeutic agents

Although beta-sitosterol (BSS) is employed primarily as a natural treatment to help control hypercholesterolemia, the glucoside of beta-sitosterol (beta-sitosterol glucoside, BSSG or sitosterolin) has not been as rigorously researched due to their low levels in human plasma. However, since 1996, Dr. PJD Bouic and his associates have investigated the immunomodulatory effects of a proprietary mixture of plant sterols and sterolins (BSS:BSSG). This combination, they determined, not only enhances the *in vivo* and *in vitro* action of T lymphocytes, but also increases the cytotoxic effects of natural killer cells against a specific cancer cell line (K562). Further experimental studies concluded that this specific sterol-sterolin mixture preferentially enhanced CD4 T_{H1} cells and therefore could restore the delicate T_{H1}:T_{H2} balance. Unfortunately, this balance is often tipped towards a predominantly T_{H2} response resulting in a poor cellular and humoral immune response. Moreover, at physiological

concentrations, this same combination of plant sterols/sterolins helped prevent the release of pro-inflammatory cytokines interleukin-6 and tumor necrosis factor alpha by 98% in endotoxin stimulated monocytes. This confirmed the results of other researchers who found that the extracts of leaves (or other parts of plants) were rich in sterols and had profound anti-inflammatory effects, which in some cases, were comparable in action to the anti-inflammatory drug hydrocortisone. Given that sterols and sterolins exhibited both immunomodulatory and anti-inflammatory actions, it was only logical that clinical trials begin with these non-toxic natural products.

Clinical studies on sterols/sterolins

Tuberculosis (TB)

In a double-blind controlled study, the use of sterols/sterolins as adjunctive therapy helped TB patients recover faster, gain more weight, and exhibit less inflammation than those taking a placebo.

Marathon Runners and Immunosuppression

In this double-blind controlled trial, marathon runners who utilized the unique sterol/sterolin mixture did not exhibit any of the typical post-event immuno-suppression (e.g. neutrophilia, leucocytosis, lymphopaenia) seen in the placebo group. Moreover, those supplementing with plant sterols/sterolins were able to inhibit the inversion of CD4:CD8 ratios thereby blunting the temporary immunosuppressive effect of the race. In addition, the cortisol/DHEA-s ratio was maintained to that of pre-event levels in runners employing the BSS:BSSG mixture.

HIV Infection

In an open label study, HIV positive patients with CD4 cell counts above 500 cells/μl blood and who were not using anti-retroviral drug therapy showed stable CD4 cells counts and a

decrease in their plasma viral loads after employing the BSS:BSSG mixture for up to 40 months. This group of patients maintained a predominantly T_{H1} profile indicating that their cell mediated immunity response accounted for both their viral control and prevention of CD4 cell loss.

Rheumatoid Arthritis

In a recent controlled trial, patients with rheumatoid arthritis (RA) had a significant reduction in their disease activity (according to American College of Rheumatology criteria) when employing the sterol/sterolin mixture. Although both the treatment group and a placebo group in this study employed anti-inflammatory (e.g. diclofenac) and analgesic (e.g. paracetamol) medications, those patients using the plant sterol/sterolin mixture had a 48% response to the treatment compared to only 21% in the placebo group. Moreover, patients in the active group utilized fewer prescription medications suggesting that their quality of life was better. Plant sterols/sterolins, the authors note, may work similarly to the product Flemun from the German Company Intermuti Pharma which decreases cyclooxygenase and lipoxygenase activity *in vivo* and *in vitro*.

Feline Immuno-deficiency Virus (FIV)

FIV infected cats treated with the sterol/sterolin mixture maintained their CD4 cell counts over long time periods and had significantly reduced mortality rates compared to untreated controls.

Allergic Rhinitis/Sinusitis

Those suffering with allergic conditions exhibit a predominantly T_{H2} profile which implies more inflammatory IL-4 secretion and hence greater release of IgE. In testing this hypothesis, 24 individuals with allergic rhinitis/sinusitis were given the sterol/sterolin mixture over a 12- week period and found to have significant reductions in their objective- (e.g. reduced rhinorrhea, post-nasal drip, nasal turbinate hypertrophy, IgE levels) and subjective clinical symptoms.

Conclusion: Although the ability to control symptoms and the inflammation arising from a disordered immune system has been the mainstay of modern medical therapy, we stand on the brink of new knowledge that certain CD4 cell subsets and their soluble messengers can have a significant impact on the course of chronic disease.

While there are numerous natural products that contain phytosterols such as Ginkgo and Cat's claw, it is only the 100:1 standardized mixture of plant sterols to sterolins that has been found to be optimal in balancing the delicate T_{H1}:T_{H2} ratio at relatively low concentrations. Sterols and sterolins may then usher in a new era of treatment in which we try to repair the underlying abnormality rather than suppress the symptoms of disease.

Rheumatoid Arthritis (RA)

Reference: Louw, I, *et al.* A pilot study of the clinical effects of a mixture of beta-sitosterol and beta-sitosterol glucoside in active rheumatoid arthritis (RA). *Am J Clin Nutr* 2002; 75(2), 351S [Abstract 40].

Study: In a controlled trial, 18 patients were randomised to receive either 20mg BSS/0.2mg BSSG capsules (Moducare®) or placebo three times a day for 24 weeks. All patients had active RA as defined by American College of Rheumatology (ACR) criteria.

Patients in both the treatment and placebo groups used anti-inflammatory and analgesic medications for the duration of the study. No new therapies could be initiated during the study. Patient response was assessed in terms of ACR response criteria (>20% improvement).

Results: In the group receiving the BSS:BSSG mixture, statistically significant changes were noted in the mean tender joint count (85% ACR response); patient's assessment of pain (28% response); patient's global assessment of disease activity (33% response); physician's global assessment of pain (47%) and the MHAQ decreased (47% response). The ESR also decreased significantly (56% response). The placebo group had no significant improvement using the ACR criteria.

Clinical Summary: Due to the potent anti-inflammatory properties of Moducare®, patients with RA may benefit from the addition of this phytosterol mixture to current management strategies.

Human Immunodeficiency Virus (HIV)

Reference: Bouic PJD, Clark A, Brittle W, Lamprecht JH, Freestone M, Liebenberg RW. Plant sterol/sterolin supplement use in a cohort of South African HIV-infected patients—effects on immunological and virological surrogate markers. *South African Med J* 2001; 91: 848–50.

Study: In an open label pilot study, 123 HIV positive patients (who were not on any retroviral medications) were given a proprietary mixture of sterol/sterolin supplement (Moducare®) on a daily basis over a period of 39 months. Subjects who participated in this study were evaluated at 0, 1, 2, 3 months and then every four months thereafter for body mass, concomitant conditions (e.g. opportunistic infections), CD4 lymphocyte cell count and viral loads. For study purposes, patients were stratified into 3 groups based on CD4 counts at the beginning of the trial: CD4 < 200/μl (n = 10), CD4 200 – 500/μl (n = 66), CD4 > 500/μl (n = 47).

Results: Patients with a CD4 count of less than 200/μl showed a significant reduction in the median percentage and absolute numbers of CD4 cells/μl from baseline values of 11% and 134 CD4/μl to 7% and 23 CD4/μl respectively after 21 months. However, despite this first group's decrease in immunologically active CD4 cells, there was no significant change in the patients' viral load from baseline (4.23 log) to the end of the trial (4.60 log) period. Similarly, patients in Group 2 whose CD4 count was between 200 – 500/μl, showed no significant changes in median CD4 percentage (19% at baseline compared to 18.5% at completion), median CD4 count (349 versus 275/μl) and plasma viral load (5.06 log in contrast to 5.15 log) during the 39 months they were evaluated.

Like the outcomes seen in the other two groups, patients in the third and most immunologically stable group (CD4 > 500/μl) exhibited no changes in their CD4 immune markers. They did

however have a significant reduction in plasma viral load of 1.48 log from 4.59 log at the beginning of the study to 3.11 log at 30 months. Moreover, 15% (7/47) of patients within this group had no detectable plasma viral count after 12 months of therapy with plant sterols/sterolins.

Clinical Summary: Although these results should be confirmed in a controlled clinical trial, HIV positive patients whose CD4 count is above 500/ μ l may be able to stabilize their CD4 cell counts and reduce their viral load through the judicious use of a plant sterol/sterolin mixture (Moducare®) at a dose of 1 capsule 3 times a day between meals.

Post-Marathon Immune Suppression

Reference: Bouic PJD, Clark A, Lamprecht J, Freestone M, *et al.* The effects of β -sitosterol (BSS) and β -sitosterol glucoside (BSSG) mixture on selected immune parameters of marathon runners: inhibition of post marathon immune suppression and inflammation. *Int J Sports Med* 1999; 20:258–62.

Study: In this controlled investigation, a group of 17 athletes (11 males, 6 females; age range 26 to 51 years) from a running club in Cape Town, South Africa were randomly assigned to one of two treatment groups four weeks prior to the 68 km Two Oceans Marathon. After randomization, runners in group B were given a BSS:BSSG mixture (20 mg BSS and 0.2 mg BSSG, Moducare®) three times a day while those in group A were given placebo capsules at the same dosing schedule. Extensive laboratory analysis including a full blood count, liver function tests, markers of immunity (CD3, CD4, etc), cortisol, and DHEA-s was performed on each volunteer at baseline and three days after completion of the marathon.

Results: A reduction in lymphocytes (lymphopenia) is common after strenuous exercise and the data presented by Dr. Bouic and associates confirms this. The percentage of lymphocytes decreased in the placebo group from 39.0 to 33.8% by the end of the trial, while those marathoners employing Moducare® remained stable in their lymphocyte count. Moreover, those using Moducare® had significant increases in CD3 and CD4 levels compared to the placebo group suggesting that these supplemented runners were less likely to be immunosuppressed after the marathon. In addition, those taking Moducare® had significant reductions in the pro-inflammatory monokine IL-6 from 225 IU/ml to 190 IU/ml post race. In contrast, the placebo group showed an increase in IL-6 from 184 IU/ml to 236 IU/ml at the end of the study.

Cortisol, an adrenal and stress-related immuno-suppressive hormone, rose significantly by 38.9 nmol/l in the placebo group but decreased slightly by 7.5 nmol/l in the active group by the conclusion of the trial. In addition, both groups experienced a non-significant increase in DHEA-s levels from 4.0 to 4.4 μ mol/l and from 4.2 to 5.0 μ mol/l in the placebo and Moducare® groups respectively. The cortisol/DHEA-s ratio in the Moducare® treated group had a significant 22.8 point reduction compared to only a 3.4 point reduction in the placebo group.

In those runners employing Moducare®, there was a non-significant increase by 4.5% in white blood cells and 5.4% in neutrophils compared to baseline values. By comparison,

placebo subjects exhibited a significant 13.6% and 23.0% increase in white blood cells and neutrophils respectively.

Clinical Summary: Although gentle exercise is known to increase immunity, strenuous exercise can temporarily suppress the immune system. Supplementation with Moducare® may help those athletes or “weekend warriors” engaged in a difficult training program from catching the flu bug by improving their immunity and decreasing the immunosuppressive inflammatory response associated with their exercise.

Allergies

Reference: Myers, L and Bouic, PJD. Flow cytometric analysis of the T_{H1} - T_{H2} shift in allergic individuals using Moducare® (sterols/sterolins). *Proc. 26th Annu Cong Physiol Soc S. Afr.* 1998; Abstract 178.

Study: A placebo-controlled blinded pilot study was performed on 24 atopic individuals (mainly pollen sensitivity) over a 12-week period. To determine whether the balance between T_{H1} and T_{H2} CD4 cells differs between allergic and non-allergic individuals, several laboratory and clinical markers of activity were measured. Four groups were followed: allergic persons were given either placebo or active Moducare® capsules and the lymphokine profile was determined at baseline and again 4 weeks later. A group of non-allergic persons serving as controls was similarly formed. Blood lymphocytes were analysed using flow cytometry.

Results: It was shown that allergic persons exhibited significantly raised IL4 containing CD4+ cells at the start of the study when compared to the non-allergic control group. The intake of Moducare® induced a significant decrease in IL4 in both allergic as well as in the control groups. It was interesting to note that, unlike the allergic persons, the non-allergic controls receiving the sterols/sterolins capsules increased their IFN- γ CD4+ cells after 4 weeks of therapy.

Statistically significant changes occurred with the allergic individuals in the following: less rhinorea, less turbinate hypertrophy, less post nasal drip symptoms, lower IgE plasma levels and higher T_{H1} producing cells. Subjective improvements were reported by the patients themselves when use of an international questionnaire was made to record patient symptoms.

Clinical Summary: The T_{H1} - T_{H2} response in allergic individuals appears perturbed when compared to that of healthy, non-allergic controls. Moducare® appears to decrease the synthesis of IL4 in allergic persons as well as in healthy controls.

Immune Modulation

Reference: Bouic PJD, Etsebeth S, Liebenberg RW, Albrecht CF, *et al.* Beta-sitosterol and beta-sitosterol glucoside stimulate human peripheral blood lymphocyte proliferation: implications for their use as an immunomodulatory vitamin combination. *Int J Immunopharm* 1996; 18:693–700.

Study: In this paper, the immunological actions of sterols/sterolins (Moducare®) were considered by both *in vitro*

and *in vivo* experiments. In the first *in vitro* study, venous blood was drawn from healthy laboratory volunteers and employed as a source of T cells. These T cells were added to cell cultures and incubated along with ³H-thymidine and stimulated suboptimally with a mitogen for 72 hours. Varying concentrations of beta-sitosterol (BSS), beta-sitosterol glucosides (BSSG), and a 100:1 ratio of BSS/BSSG (Moducare®) were then added to these mixtures and laboratory markers of immune response such as T cell proliferation, CD25 and HLA-DR activation, IL-2 secretion, gamma interferon release, and natural killer (NK) cell activity were recorded.

In the *in vivo* portion of the trial, six volunteers ingested one capsule of Moducare® (20mg BSS and 0.2mg BSSG) 3 times a day for four weeks. Two volunteers were given placebo capsules at the same dosing schedule. Blood samples were collected at 0, 1, 2 and 4 weeks. The resulting T cells were incubated with ³H-thymidine and stimulated maximally with the PHA mitogen allowing the researchers to evaluate T cell proliferation at baseline and day 30.

Results: *In vitro* results demonstrated that although both phytosterols (BSS and BSSG) enhance the proliferative response of T cells to mitogen stimulation at very low concentrations, a 100:1 ratio of BSS to BSSG provided a larger stimulatory effect than could be achieved by the individual phytosterols and sterolins alone. Moducare® at a concentration of 1 µg/ml was able to double the expression of CD25 and HLA-DR activation antigens on T cells, and increase the secretion of IL-2 (ranging from 17 to 23%) and gamma interferon (ranging from 36 to 41%) compared to controls. In addition, the combination of BSS/BSSG (100:1) at 1 µg/ml was consistently more active at stimulating the lytic action of NK cells (effector) on a cancer K562 cell line (target) than BSS or BSSG on their own. Different effector:target ratios were tested ranging from 12,25,50 and 100:1 and for all these cell ratios the BSS/BSSG stimulated NK cells were the most effective.

In vivo results from the eight volunteers concluded that compared to baseline values, T cell proliferative responses increased from 20 to 920% in those taking Moducare® over 4 weeks compared to a relatively unchanged (-2 to 13%) reaction in the placebo group.

Clinical Summary: The unique combination of plant sterols/sterolins as found in the product Moducare® significantly enhances the laboratory markers of immunity both *in vitro* and *in vivo*.

Benign Prostatic Hyperplasia (BPH)

Reference: Berges RR, Windeler J, Trampisch HJ, *et al.* Randomized, placebo-controlled, double-blind clinical trial of β-sitosterol in patients with benign prostatic hyperplasia. *Lancet* 1995; 345(8964):1529-32.

Study: In this double-blind clinical trial, 200 male patients (average age 65 years) with symptoms of benign prostatic hypertrophy, were randomized to receive 20 mg β-sitosterol plus 0.2 mg β-sitosterol glucoside or placebo three times a day for 6 months. The product employed in the trial was Harzol™ (distributed by Hoyer GmbH and Co, Germany) with each

capsule containing 10 mg β-sitosterol and 0.1 mg β-sitosterol glucoside. Primary assessment of the study's outcomes was performed using a modified Boyarsky scale at monthly intervals. Secondary outcomes including International Prostate Symptom Score (IPSS), urine flow, residual urine volume, and other parameters of urinary flow plus prostate size were measured at 3 and 6 months. Laboratory values such as PSA, complete blood cell counts and a urine culture were performed at baseline and the conclusion of the study.

Results: Those patients employing β-sitosterol and its glucoside had a significant reduction in their Boyarsky scores with an average decrease of 6.7 points compared to only 2.1 points in the placebo group after 6 months of therapy. IPSS scores also decreased in a similar fashion with average reductions of 7.4 and 2.1 points in the active and placebo groups respectively. This reduction in Boyarsky and IPSS scores were paralleled by the changes in urinary flow characteristics. For example, those patients employing Harzol™ not only had an increase in peak urinary flow from 9.9 to 15.2 ml/s but also experienced a reduction in mean residual urinary volume from 65.8 to 30.4 ml/s after 180 days of treatment. In addition, average voiding time decreased by 15.5 seconds in those utilizing Harzol™ compared to 2.8 seconds in the placebo group. Prostate volume was not affected in either group.

Clinical Summary: Both the Harzol™ and Moducare® products have their origins with the company Essential Sterolin Products in Midrand, South Africa. The Harzol™ product employed in this study by Berges *et al* contains the same active ingredients as found in Moducare®, namely β-sitosterol and β-sitosterol glucoside in a 100:1 ratio. However, unlike Harzol™, each Moducare® capsule contains twice as much of the active ingredient (e.g. 20 mg β-sitosterol and 0.2 mg β-sitosterol glucoside). Thus patients with BPH may experience a significant change in their symptoms (e.g. better urinary flow, less urinary retention, and fewer night time awakenings) by employing the product Moducare® at a dose of one capsule three times a day for at least 6 months.

Additional Research

Bouic, PJD: The role of phytosterols and phytosterolins in immune modulation: a review of the past 10 years. *Curr Opin Clin Nutr Metab Care* 2001; 4,471-475.

Breytenbach, U. *et al*: Flow cytometric analysis of the Th1-Th2 balance in healthy individuals and patients infected with the human immunodeficiency virus (HIV) receiving a plant sterol/sterolin mixture. *Cell Biol Int* 2001; 25, 43-49.

Bouic, PJD and Lamprecht, JH: Plant sterols and sterolins: a review of their immune-modulating properties". *Alt Med Rev* 1999; 4:170-177.

Pegel, KH: The importance of sitosterol and sitosterolin in human and animal nutrition". *S A J Sci* 1997; 93: 263-268

Donald PR, *et al*: A randomised placebo-controlled trial of the efficacy of beta-sitosterol and its glucoside as adjuvants in the treatment of pulmonary tuberculosis. *Int J Tuberc Lung Dis* 1997; 1: 518-22

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