

Keywords

Erectile dysfunction

BIOVIS[®]*Tribulus terrestris*Alga *Ecklonia bicyclis*

Phytotherapy

Phytomedicine

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Analyzing the efficacy of a new natural compound made of the alga *Ecklonia bicyclis*, *Tribulus terrestris* and BIOVIS[®] in order to improve male sexual function

F. Iacono, MD
School of Medicine and Surgery, University "Federico II", Naples, Italy

D. Prezioso, MD
School of Medicine and Surgery, University "Federico II", Naples, Italy

A. Ruffo, MD
School of Medicine and Surgery, Department of Urology, University "Federico II", Via S.Pansini 5, Naples, Italy 80131

G. Di Lauro, MD
Hospital Santa Maria delle Grazie, Pozzuoli, Naples, Italy

L. Romis, MD
Hospital Santa Maria delle Grazie, Pozzuoli, Naples, Italy

E. Illiano, MD
School of Medicine and Surgery, University "Federico II", Naples, Italy

E-mail:
antonio.ruffo7@gmail.com

F. Iacono, D. Prezioso, A. Ruffo, G. Di Lauro, L. Romis and E. Illiano

Abstract

Background: We investigated the therapeutic efficacy of a new composite natural drug based on *Tribulus terrestris*, BIOVIS[®] and the alga *Ecklonia bicyclis* in order to improve male sexual function, selecting patients using the International Index of Erectile Function (IIEF), Nocturnal Penile Tumescence and Rigidity Testing (NPTR) using the RigiScan[®] device and hormonal levels.

Materials and methods: A total of 164 patients with erectile dysfunction (ED) were enrolled between September 2009 and January 2010. Patients were classified as having mild ($n = 64$), moderate ($n = 62$) or severe ($n = 38$) ED. Mean age was 53.1 years. A new compound (150 mg of the alga *Ecklonia bicyclis*, 396 mg of *Tribulus terrestris* and 144 mg of BIOVIS[®]) was administered to all patients twice a day for 60 days. The IIEF questionnaire was administered and NPTR testing was carried out using the RigiScan[®] device both pre and post-treatment with all patients.

Results: 150 patients were evaluable, and their IIEF scores were all significantly improved, with an increase of 78% in the mild ED group, an 80% improvement in the moderate ED group, and an improvement of 108% in the severe ED group compared with the baseline. The mean IIEF scores for all the patients showed significant improvement after 8 weeks of treatment with this new composite drug (baseline 14.3 ± 1.5 to 26.2 ± 3.2 ; $P = 0.01$). Among other parameters penile rigidity and tumescence, as tested using the RigiScan[®] showed significant improvement for treated patients. Furthermore, no significant side effects were claimed.

Conclusion: The active components of these three natural compounds (namely protodioscin, a steroidal saponin, contained in *Tribulus terrestris*; the polyphenols, dieckol, florofucofuroeckol and bieckol, contained in the alga *Ecklonia bicyclis*; and the polymers of *d*-glucosamine and *n*-acetyl-*d*-glucosamine contained in BIOVIS[®]) when combined, seem to work in synergy not only improving erectile function but also stimulating testosterone-dependent sexual desire. Protodioscin is able to stimulate testosterone production and it also has an androgen-mimetic action, binding and activating the testosterone receptors. Polyphenols play an anti-inflammatory role, modulating the cytokines (lipopolisaccarids, TNF-alpha, IFN-gamma) with a potent antioxidant and antifibrotic effect. BIOVIS[®] acts on both the

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non-adrenergic and non-cholinergic system (NANC) and on the endothelial cell system as a strong nitric oxide synthetase (NOS) stimulator. Our study demonstrated that this new composite drug was effective in the oral treatment of ED. © 2011 WPMH GmbH. Published by Elsevier Ireland Ltd.

Introduction

The pharmacological treatment of erectile dysfunction (ED) has become a major tool in the therapeutic approach to impotence. This example of successful therapy largely depended on advances in clinical and basic research, which focused on the local mechanisms of penile erection. The introduction of oral phosphodiesterase-5 inhibitors (PDE5-i) in the late 1990s and early 2000s revolutionized the field of sexual medicine, having the great worth of inducing an erection in many men suffering the problem of ED, thus being an effective treatment of this disease. In fact, PDE5-i have become the most popular treatment and are currently the first-line monotherapy for ED, indicating that most patients prefer oral therapy [1]. However, a significant proportion of patients with complex ED will be therapeutic non-responders to PDE5-i monotherapy [2]. Furthermore, these drugs present various problems for the wide spectrum of co-morbidities in patients with ED [3], in particular the daily use of anti-hypertensive drugs in patients with cardiovascular disease can lead to dangerous side-effects [4].

Furthermore, the frequently reported side-effects, such as headache, muscular pains, hot flushes, tearing and so on, can affect normal sexual intercourse [3]. However, approximately 30% of patients are unresponsive to on-demand PDE5-i regimens due to both psychogenic and organic factors [5]. Also, after the initial enthusiasm, the psychological impact – artificial erections and “planning” for sexual intercourse – as well as a not yet proven curative effect, has limited the use of these drugs, leaving the field open for the further development of more natural drugs for improving male sexual function.

One such natural drug is based on a new composite of *Tribulus terrestris*, BIOVIS[®] and the alga *Ecklonia bicyclis*, all of which are used in many countries under different dosage regimens for the purpose of stimulating sexual function, although only a few studies have been carried out on their efficacy [6]. The

combination of the active principles present in these three natural compounds work in synergy and have been shown, in our preliminary data [7], to have good efficacy for oral therapy of ED. In this study we investigated whether this new natural compound based on the alga *Ecklonia bicyclis*, *Tribulus terrestris* and BIOVIS[®] at an elevated dosage would be truly beneficial in improving male sexual function, according to currently available parameters including the International Index of Erectile Function (IIEF) score, hormonal levels, and Nocturnal Penile Tumescence and Rigidity (NPTR) score as tested using a Rigiscan[®].

Materials and methods

Between September 2009 and January 2010, 164 patients with ED and without previous treatment for their ED were assessed for study inclusion. Exclusion criteria were a history of radical prostatectomy or spinal cord injury, serious neurological deficits such as multiple sclerosis and Parkinson's disease, genital abnormality, alcohol or drug abuse, a history of hormonal therapy, androgen ablation or cancer chemotherapy, previous use of nitrate drugs and a severe vasculogenic impotence. Patients with concomitant medical diseases were included in our study if they had stable disease with concurrent medical therapy for cardiovascular disease, diabetes and so forth.

The medical and psychosexual history of all patients was evaluated at baseline to detect co-morbidities. Organic co-morbidities included hypertension in 46 patients (28.1%), diabetes in 24 (14.6%) and abnormal total serum cholesterol in 14 (8.5%).

Furthermore, the IIEF questionnaire was administered to each patient and the baseline serum level of testosterone was checked. After completing the IIEF questionnaire, the patients were divided into three groups:

- 1) Group A: 64 patients (36.6%) classified as having mild ED (IIEF score >16).

Table 1 Pre and post-treatment scores for each ED group

	IIEF (total score)	Area 1	Area 2	Area 3	Area 4	Area 5
Group A						
Pre-treatment	22.1 ± 1.6	5.8 ± 0.4	5.3 ± 0.4	4.1 ± 1.7	4.3 ± 1.0	2.5 ± 0.8
Post-treatment	39.3 ± 5.1	11.2 ± 2.0	5.91 ± 1.6	8.7 ± 1.2	7.1 ± 1.9	6.3 ± 1.5
Group B						
Pre-treatment	14.1 ± 1.5	4.7 ± 1.2	2.4 ± 0.8	3.0 ± 0.9	1.8 ± 0.4	2.2 ± 0.4
Post-treatment	25.4 ± 1.8	8.4 ± 1.6	2.9 ± 1.0	7.5 ± 1.1	3.1 ± 0.9	3.6 ± 0.7
Group C						
Pre-treatment	6.7 ± 1.4	1.8 ± 0.9	0.0 ± 0.0	2.3 ± 0.7	0.6 ± 1.7	2.1 ± 0.3
Post-treatment	13.9 ± 2.0	3.3 ± 1.1	0.5 ± 0.9	6.0 ± 1.7	1.6 ± 1.0	2.6 ± 0.6

Patients were divided into Group A, mild ED (IIEF score ≥ 16); Group B, moderate ED (IIEF score between 11 and 16); and Group C severe ED (IIEF score ≤ 19). Area 1, erectile function; Area 2, orgasmic function; Area 3, sexual desire; Area 4, intercourse satisfaction; Area 5, overall satisfaction.

- 2) Group B: 62 patients (35.4%) classified as having moderate ED (IIEF score between 11 and 16).
- 3) Group C: 38 patients (19.5%) classified as having severe ED (IIEF score < 10) [8].

For each group we report: erectile function (Area 1), orgasmic function (Area 2), sexual desire (Area 3), intercourse satisfaction (Area 4), and overall satisfaction (Area 5) (see Table 1)

Furthermore, all patients were examined using penile dynamic Doppler ultrasonography and tested for NPRT using the RigiScan[®] device (UroHealth Systems, Laguna Niguel, California) to determine baseline parameters including rigidity, and number and duration of nocturnal penile erections [9].

After the baseline evaluation, all patients were treated for 8 weeks with this new natural composite drug (150 mg of the alga *Ecklonia bicyclis*, 396 mg of *Tribulus terrestris* and 144 mg of BIOVIS[®] per tablet) twice a day.

After treatment, the IIEF questionnaire was again administered, testosterone levels were recorded and NPTR measured.

The Mann-Whitney test was used to determine the statistical significance of responses to the global efficacy question, and the paired Student *t*-test was used for other statistical comparisons, $P < 0.01$ was considered significant.

Results

During the treatment there were 14 drop-outs: 4 patients (2.4%) quit the therapy due to mild gastrointestinal side effects (stomach ache, 3 patients; diarrhea, 1 patient); 6 patients (3.6%)

had low compliance; 2 patients (2.4%) stopped due to insomnia; and 2 patients dropped out due to personal concerns.

At the end of the treatment there were 150 evaluable patients. The mean age was 53.1 ± 8.2 years. Table 1 reports the improvement in the IIEF score after 60 days of treatment in each of the three groups for these 150 evaluable patients.

Group A showed an improvement in all domains of the IIEF questionnaire scores, with a significant improvement after 8 weeks of treatment (from a baseline total score of 22.1 ± 1.6 to a final score of 39.3 ± 5.1 ; $P < 0.01$). Group B also showed a significant improvement in all domains of the IIEF questionnaire after 8 weeks of treatment (from a baseline score of 14.1 ± 1.5 to a final score of 25.4 ± 1.8 ; $P < 0.01$). Finally, Group C showed a similar improvement in all IIEF domains, with mean IIEF score after 8 weeks of treatment improving from the baseline value of 6.7 ± 1.4 to a final score of 13.9 ± 2.0 ($P < 0.01$) (see Table 1) [8].

The mean baseline values for the three RigiScan[®] items (number of nocturnal erections, rigidity of the penis measured on a percentile scale of penile tumescence, and duration of the nocturnal erections) as well as the changes in the RigiScan[®] scores after the treatment in the 150 evaluable patients [9] are reported in Table 2. The mean values of the RigiScan parameters after 8 weeks of therapy revealed, in all three groups, significant ($P < 0.01$) increases in the number of nocturnal erections and in the percentile scale value for penile tumescence. In fact, the RigiScan[®] scores showed improvement in 93.7% of the population. Specifically,

Table 2 Pre and post-treatment *Rigiscan*[®] scores

	Number of erections (N ^o)	Rigidity (%)	Duration (min)
Group A			
Pre-treatment	3.5 ± 0.9	70.5 ± 4.2	13.7 ± 1.4
Post-treatment	4.1 ± 0.7	78.1 ± 5.0	14.0 ± 1.6
Group B			
Pre-treatment	1.8 ± 0.7	62.6 ± 3.6	9.6 ± 1.4
Post-treatment	2.5 ± 0.5	66.6 ± 2.8	10.0 ± 1.3
Group C			
Pre-treatment	0.8 ± 0.4	44.3 ± 20.8	5.2 ± 3.0
Post-treatment	1.4 ± 0.5	61.2 ± 2.9	6.3 ± 2.2

in Group A, a 17% increase in the number of spontaneous erections and an 11% increase in the mean percentage of rigidity was found. In Group B, there was a 39% improvement in the number of erections and a 6% improvement in percentage rigidity. Finally, in Group C the number of erections increased by 75% and there was a 38% increase in penile rigidity score (Table 2)

Testosterone levels also improved in the group affected by mild ED (A), from a baseline mean value of 5.3 ± 1.1 ng/ml (normal range = 2.8–9.8 ng/ml) [10], to 6.8 ± 1.6 ($P < 0.01$) post-treatment, an improvement of 28%. Patients suffering from moderate ED (Group B) showed a 24% increase in serum testosterone levels, from a baseline mean value of 5.0 ± 1.1 ng/ml to 6.0 ± 1.2 ($P < 0.01$). Finally, in those with severe ED (Group C) mean testosterone level improved by 24%, from 5.0 ± 1.0 ng/ml at baseline to 6.2 ± 1.3 ng/ml at the end of treatment ($P < 0.01$) (Table 3).

Finally, the mean serum level of total prostate-specific antigen (PSA) was measured at

Table 3 Pre and post-treatment changes in mean serum testosterone levels

	Testosterone (ng/ml)
Group A	
Pre-treatment	5.3 ± 1.1
Post-treatment	6.8 ± 1.6
Group B	
Pre-treatment	5.0 ± 1.1
Post-treatment	6.0 ± 1.2
Group C	
Pre-treatment	5.0 ± 1.0
Post-treatment	6.2 ± 1.3

Table 4 Pre and post-treatment serum PSA levels

	PSA (ng/ml)
Group A	
Pre-treatment	1.8 ± 0.6
Post-treatment	1.8 ± 0.3
Group B	
Pre-treatment	1.9 ± 0.2
Post-treatment	1.9 ± 0.5
Group C	
Pre-treatment	1.8 ± 0.1
Post-treatment	1.7 ± 0.9

baseline and after treatment. Mean PSA level at baseline was 1.8 ± 0.6 (normal range = 0–4 ng/ml) in Group A, 1.7 ± 0.6 in Group B and 1.8 ± 0.7 in Group C. There was no statistically significant difference in PSA level after treatment in any of the patient groups (Table 4).

Discussion

In this study we attempted to evaluate the effectiveness of a combination of *Tribulus terrestris*, the alga *Ecklonia bicyclis* and BIOVIS[®], all contained in a new natural compound, for the management of male sexual dysfunction.

This new natural compound is thought to play an important double role (therapeutic and anti-aging), on cavernous tissue, by acting on the etiopathogenetic aspects of ED, mainly the microstructural alteration of the corpus cavernosum tissues, following inflammation and/or oxidative damage [11].

Tribulus terrestris contains flavonoids, alkaloids and amides, although its properties seem to be completely attributed to protodioscin.

The parts used are the seeds and fruits, and, more generally, the aerial parts of the plant. Protodioscin is a steroidal saponin, which forms about 45% of the extract obtained from the aerial parts of *Tribulus terrestris*. Due to its chemical structure this substance has an androgen-mimetic action, binding and activating the testosterone receptors, and it is able to increase the endogenous production of testosterone, dihydrotestosterone, luteinizing hormone (LH) [12], dehydroepiandrosterone (DHEA) and dehydroepiandrosterone sulfate (DHEA-S) [13]. Because of these effects, in experimental animals there is an increase in spermatogenesis and the frequency of matches [14]. In the rabbit, in particular, it has been shown that the compound stimulates the release of nitric oxide (NO) by the vascular endothelium of the corpora cavernosa, thereby having a pro-erectile effect [15,16]. The mechanism behind this effect appears to involve the steroid hormones' pathway. Protodioscin has been used in humans. A study conducted on 406 Chinese patients with angina pectoris showed that protodioscin may be a useful treatment for this cardiac pathology as it is associated with a dilation effect on the coronary arteries [17].

Dieckol, florofucofuroeckol and bieckol are phlorotannins, and are found at very high concentrations in the crude polyphenol fractions of the alga *Ecklonia bicyclis*. Their scavenger activity is 10–100 times more powerful than any other polyphenol from *T. terrestris* plants, including the green tea catechins, which have only 3–4 phenolic rings, that are commonly considered to be among the most effective antioxidant molecules. These properties are due to the fact that phlorotannins are fat-soluble at 40% so they have a longer half-life and action (12 hours) [18] compared to common polyphenols, which are water-soluble and have a relatively short half-life once introduced into the body. In *Ecklonia bicyclis* there are molecules that are able to reduce the inflammatory response, partially neutralizing the inflammatory damage caused by reactive oxygen species (ROS), in part by slowing the lipoxygenase pathway and inhibiting the formation of prostaglandin E₂, a powerful

inflammatory mediator. Furthermore, *Ecklonia bicyclis* suppresses proinflammatory cytokines such as lipopolysaccharids, tumor necrosis factor (TNF)-alpha, and interferon (IFN)-gamma, thus carrying out a potent antioxidant [19] and antifibrotic effect [20]. BIOVIS[®] contains polymers of *d*-glucosamine and *n*-acetyl-*d*-glucosamine, which both act on the non-adrenergic and non-cholinergic system (NANC) and on the endothelial cell system as a strong nitric oxide synthetase (NOS) stimulator, thus improving the concentration of nitric oxide (NO) in the smooth cells inside the corpus cavernosum [21].

Conclusion

The most frequent requirement by men affected by ED is a product – preferably natural rather than synthetic – that will work with a progressive action to improve their sexual function, that has a curative and not just a symptomatic action, and that also improves sexual desire and has a potentially anti-aging action. This product should not have any significant side effects and should be compatible with the consumption of other drugs.

The use of PDE5 inhibitors is often linked to many side effects, which negatively influence the entire experience of sexual intercourse [2].

The use of a natural product, free from side effects, that has got real efficacy on erection quality and on sexual desire, could be the right way to cure and prevent male sexual and erectile dysfunction.

The compound used in our study, made from the alga *Ecklonia bicyclis*, *Tribulus terrestris* and BIOVIS[®], has shown a significant efficacy in producing an improvement in both erection and sexual desire in the majority of the patients we treated.

However, more clinical and histological research is necessary to evaluate the efficacy of this new drug in inhibiting degenerative changes with fibrosis and loss of smooth muscle in the corpora cavernosa in the ageing male [22], in patients who have undergone radical prostatectomy [23] and in patients affected by induratio penis plastica or Peyronie's disease [24].

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