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Physiological Aspects of Male Libido Enhanced by Standardized *Trigonella foenum-graecum* Extract and Mineral Formulation

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The aim of the clinical study was to evaluate the effect of Testofen, a standardized *Trigonella foenum-graecum* (Fenugreek) extract and mineral formulation, on male libido (sexual drive, urge or desire) in a double blind randomized placebo controlled study. The study recruited 60 healthy males aged between 25 and 52, without erectile dysfunction and randomized to an oral dose (two tablets per day) of the active treatment (600 mg Testofen per day) or placebo for 6 weeks. The primary outcome measure was the DISF-SR (male) self-administered QOL total score and the four domain scores. The secondary outcome was specific quality of life parameters. Testofen had an overall positive effect on physiological aspects of libido. In particular, there was a significant increase in the subdomains of sexual arousal and orgasm. Testofen had a positive effect on QOL in self-reported satisfaction with muscle strength, energy and well-being but did not have an effect on mood or sleep. Serum prolactin and testosterone levels remained within the reference range. It was concluded that Testofen demonstrated a significant positive effect on physiological aspects of libido and may assist to maintain normal healthy testosterone levels. Copyright © 2011 John Wiley & Sons, Ltd.

Keywords: libido; *Trigonella foenum-graecum*; fenugreek; nutraceuticals; reproductive health; Testofen.

INTRODUCTION

Low libido is often described as a lack of interest in sexual activity, low sex drive, lack of urge or desire and is not to be mistaken with erectile dysfunction, impotence or infertility. Men who report experiencing erectile dysfunction have normal levels of desire but cannot physically act on those desires, whereas men with low sex drives can perform sexually but do not have the desire to do so.

The Global Study of Sexual Attitude and Behaviours conducted on 27500 men and women in 30 countries indicated that a lack of interest or desire in sexual intercourse was reported by 18% of men, and that a lack of pleasure from sexual intercourse was reported by 11% of the participating men (Brock *et al*., 2003). The cause of low sexual drives is not always obvious. It can be the result of psychological issues, physical conditions or combinations of a number of other factors. Psychological factors can include stress, distractions, depression, abuse or trauma as well as body image issues. On a physiological level, factors that disrupt normal hormonal balance are most likely caused by low levels of testosterone, poor fitness, being overweight or obese, malnourished, excessive alcohol intake, chronic stress (adrenal depletion) or other endocrine issues such as hypothyroidism, diabetes and hyperprolactinaemia. It is also noteworthy that medications such as diuretics and antidepressants can reduce libido (Tom, 2006).

It is now recognized that oestrogen/testosterone ratios are important in influencing libido, with oestrogen therapy inhibiting libido (females) and androgen therapy having a positive effect on libido in both males and females. The benefits of testosterone replacement therapy in men with documented hypogonadism are well recognized, with improved body composition (increased lean body mass, enhanced muscle, diminished visceral fat), mood, cognition and sexual function (Miner *et al*., 2008; Beg *et al*., 2008; Gruenewald and Matsumoto, 2003; Zhang *et al*., 2006). More recently, it was shown that statin therapy was associated with lower testosterone, prolactin and symptoms of hypogonadism (Corona *et al*., 2010).

In recent years, there has been significant interest in a herbal medicines traditionally used to improve sexual function and performance. *Ginkgo biloba* has been shown to be effective for antidepressant-induced sexual dysfunction, possibly through improved circulation and prostaglandin agonist effects or neurotransmitter and nitric oxide second messenger modulation (Cohen and Bartlik, 1998). Research has also shown that *Panax ginseng* enhances the libido possibly through its effects on the CNS and gonadal tissues as well as increasing stamina during intercourse (Jai *et al.*, 2009).

Trigonella foenum-graecum is rich in the steroidal saponins including diosgenin, yamogenin, gitogenin, tigogenin and neotigogens. Diosgenin is an important precursor for the synthesis of a number of sex hormones, and has been shown to exhibit oestrogenic effects (Aradhana *et al*., 1992). Sreeja *et al.* (2010) has since demonstrated that *Trigonella foenum-graecum* seed

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extract has oestrogenic activity, binding to oestrogen receptors and inducing the expression of oestrogen responsive genes. *Trigonella foenum-graecum* also contains other therapeutically active constituents, including choline and trimethylamine, retinol, vitamin D, riboflavin, pyridoxine and essential oils (Blumenthal *et al.*, 2000; Varjas *et al.*, 2010).

Trigonella foenum-graecum has been used in conditions including diabetes and dyslipidaemia. Efficacy and safety of this herb has been established by various clinical trials and supported by subsequent reviews (Basch *et al.*, 2003; Thompson Coon and Ernst, 2003). More recent research demonstrated that diosgenin present in fenugreek improves glucose metabolism by promoting adipocyte differentiation and inhibiting inflammation in adipose tissues (Uemura *et al.*, 2010). An unpublished randomized double blind study, by Gencor Pacific, on the same extract demonstrated that it had a positive effect on anabolic activity (as evidenced by BUN reduction) as well as significant increase in free testosterone and creatinine, compared with placebo, in a group of healthy exercising males. This supports a previous unpublished animal study, by SL Bodhankar, of the same standardized extract demonstrating an increased aphrodisiac activity and increased serum testosterone levels. Interestingly, traditional Chinese herbalists used *Trigonella foenum-graecum* for kidney problems and conditions affecting the male reproductive tract (Escot, 1995).

The current study was designed to evaluate the effects of a formulation containing the Testofen brand of *Trigonella foenum-graecum* extract combined with magnesium, zinc and pyridoxine on healthy males with low libido without sexual dysfunction.

MATERIALS AND METHODS

Recruitment. The participants were recruited through local media advertising and clinical trial databases. All participants were healthy heterosexual males 25–52 years of age interested in increasing libido. These men reported that they were not experiencing sexual dysfunction. The inclusion criteria consisted of heterosexual males 25–52 years of age, who were in a stable sexual relationship and sexually active for at least 6 months and had an anticipated stable sexual relationship for the following 8 weeks. The exclusion criteria included any physical disability that could have potentially limited sexual function, receiving any treatment/therapy for any sexual disorder during the past 6 months, prescribed coumadin (warfarin), heparin, daltaparin, enoxaparin or any other anticoagulant therapy, prescribed levodopa for Parkinson's disease or calcipotriene for psoriasis, diagnosed with hypertension and prescribed antihypertensive medications, diagnosed severe renal and/or hepatic insufficiency, genital anatomical deformities, uncontrolled diabetes mellitus, history of spinal cord injury, uncontrolled psychiatric disorder and abnormal secondary sexual characteristics. It also included diagnosed prostatic cancer or benign hypertrophy, history of genital surgery, current or history of chronic alcohol and/or drug abuse, suspected or diagnosed chickpea allergy and participation in any other clinical trial during the past 30 days.

Screening and randomization. Potential participants were screened via telephone, then requested to attend an information session where they were informed of the trial process and asked to provide their consent prior to further involvement in the trial. Consenting participants had a case history taken and underwent a brief medical assessment and blood samples taken for prostate specific antigen (PSA), full blood count (FBC), testosterone and prolactin.

The randomization of the active treatment and placebo was performed using random allocation software. Randomization was based on a total of 60 subjects, randomly allocated into two arms of equal numbers of subjects ($n=30$ for each group). There were no other criteria for randomization, however, the active treatment and placebo groups were found to be comparable in BMI and age. Both the active treatment product and the placebo product were enclosed in tablet bottles that were identical in function and appearance and individually coded. The active and placebo tablets were coated in opadry II white and carnuba wax and were not printed or stamped with identifying markings in order to minimize identifiable tablet odour, appearance, texture, hardness and other unique physical properties.

The active treatment product was a tablet-form herbal formulation containing 300 mg of Testofen brand *Trigonella foenum-graecum* extract powder supplied by Gencor Pacific Ltd, 17 mg magnesium, 15 mg elemental zinc and 5 mg pyridoxine and the excipients microcystalline cellulose, calcium hydrogen phosphate and other pharmaceutical grade excipients. The placebo product contained 50 mg rice bran and the excipients microcrystalline cellulose, calcium hydrogen phosphate and other pharmaceutical grade excipients.

Outcome measures. The primary outcome was efficacy of the treatment using the DISF-SR (males), the self-report version of the Derogatis interview for sexual functioning-self report. The DISF-SR is a set of 21 questions, split into four domains: sexual cognition/fantasy (SC), sexual arousal (SA), sexual behaviour/experiences (SB) and orgasm (O); and is designed to measure the quality of sexual function (Derogatis and Mellisaratos, 1979). All subjects completed this questionnaire at the start of the trial to provide a baseline response, and at weeks 3 and 6. For the first three domains, SC, SS and SB, the participants gave a response in the range 0–8 for each of the five questions. For the fourth domain (O), the participants were asked to give a response from 0–4 for each of the six questions.

The hormone profile was also collected; FBC and PSA (at baseline only) and serum testosterone and serum prolactin at baseline and 6 weeks. There is some evidence to suggest high levels of serum testosterone may affect serum haematocrit and PSA levels; therefore these markers have been included as surrogate safety markers. Elevated serum prolactin levels have been associated with lowered sexual desire and erectile dysfunction and may act as a negative-feedback control for sexual drive; therefore serum prolactin has been included to identify a potential confounder of the study results.

A secondary outcome was a quality of life (QOL) assessment, on a 5-point satisfaction scale, taken at baseline and at 6 weeks, rating the participants'

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satisfaction with libido, performance, muscle, strength, energy, and stamina, mood and sleep. Participants were monitored for compliance with the protocol by a combination of telephone and e-mail communications.

Statistics. The DISF-SR (males) is constructed to have a population mean score of 50 and a population standard deviation of 10. The test–re-test reliability is documented as approximately 0.8, which implies an error standard deviation in the analysis of covariance of approximately 4.5 (assuming that 80% of the test variance is explained by correlation with the pre-test result). Given a Holm's corrected test procedure, the minimal detectable effect size for the sample size is 3.86 (Holm, 1979). In a study of pre-treatment sexual health in prostate cancer, Zinreich *et al.* (1990) identified that a score of 48 (i.e. a difference of 2 from the population mean) is functionally normal. The study has therefore been powered to detect a between-group difference of 4.

Efficacy analyses were based on changes in questionnaire response scores from baseline at both 3 and 6 weeks. For each time point, the following comparisons were made for each question score, each domain sub-total, and the overall total of the 21 questions: (a) change in active treatment subjects; (b) change in placebo subjects; and (c) difference in change from baseline between active treatment and placebo subjects.

Efficacy was demonstrated if the change from baseline was significantly greater for the active treatment than for the placebo. The model used was a repeated measures analysis of variance, with 'Time' and 'Treatment' (active treatment and placebo) as fixed effects and 'Subject' as a random effect. Parameter estimates were obtained using REML (Patterson and Thompson, 1971), as implemented by Pinheiro and Bates (2000). Because of the large number of responses for each subject, multiplicity adjustments were required to avoid type I error rate inflation. Strong control of the family-wise type I error rate was achieved using Holm's method (Holm, 1979). Holm's method is a step-down Bonferroni adjustment, which stochastically dominates the Bonferroni procedure. The changes in the QOL questionnaires and testosterone and prolactin measurements between baseline and week 6 were analysed in the same manner.

The trial was assessed and approved by the Ethics Committee of the Queensland Clinical Trial Network (QCTN).

RESULTS

Demographics

Initially, 60 men were recruited into the study, with 54 participants completing the study, 27 in each arm. There were six withdrawals; three each from the active treatment and the placebo groups. The study group consisted of men aged between 25 and 52 years, with the average age being 41.3 years (STD 6.1). There was no difference between the average age of those on active treatment and placebo (41.1 and 41.6 years, respectively). The BMI for the two groups were similar (active treatment 26.7 and placebo 28.6).

Data Analysis

The result for the Total DISF-SR score was based on changes in total score across all 21 questions (Fig. 1). It takes into account all four areas of libido; sexual cognition/fantasy, sexual arousal, sexual behaviour/experiences, and orgasm. For both the 3 and 6 week time-points, the estimate, standard error, p-value and Holm adjusted p-value are shown for the change in score for active treatment subjects, change in score for placebo subjects, and the difference in change from baseline between active treatment subjects and placebo subjects (Table 1).

There are statistically significant increases in Total DISF-SR score for active treatment subjects and statistically significant interactions at both the 3 weeks (67.59 to 75.67; $p<0.01$) and 6 week time-points (67.59 to 82.48; $p<0.01$). There is a statistically significant decrease in Total DISF-SR score for placebo subjects at the 6 week time-point (72.93 to 66.81; $p<0.01$).

DISF-SR domain sub-scores: Table 2 and Fig. 2 shows the results for the analysis based on changes in sub-total scores for each domain. For each of the four domains, at both 3 weeks and 6 weeks, the estimate, standard error, p-value and Holm adjusted p-value are shown for the change in score for active subjects, change in score for placebo subjects, and the difference

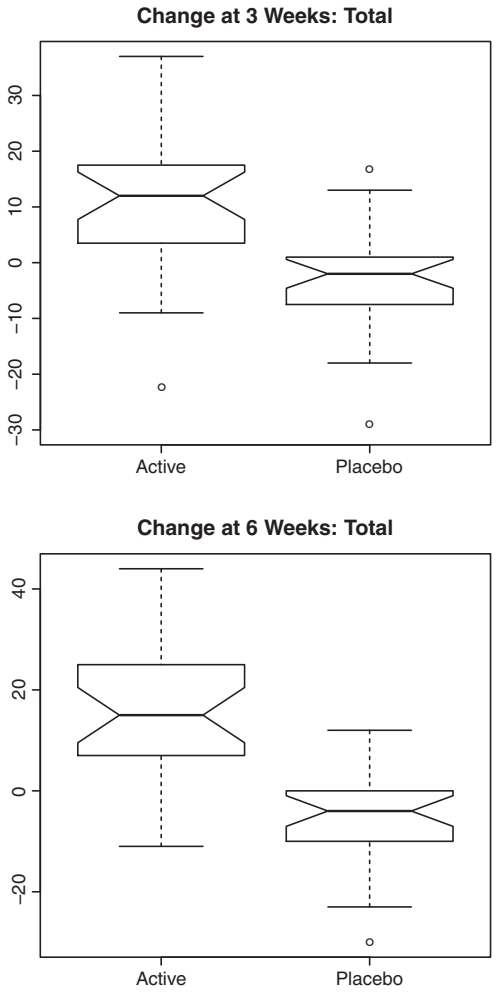

Figure 1. Changes from baseline for Total DISF-SR Score for participants on active treatment and placebo at week 3 and week 6.

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Table 1. Total DISF-SR change score for participants on active treatment and placebo at week 3 and week 6

Variable	Time difference	Term	Estimate	SE	*p* value	Adjusted *p* value
Total	3 weeks	Interaction	−13.852	3.114	0.000	0.000
Total	3 weeks	Change: Active	10.889	2.202	0.000	0.000
Total	3 weeks	Change: Placebo	−2.963	2.202	0.184	0.184
Total	6 weeks	Interaction	−22.074	3.213	0.000	0.000
Total	6 weeks	Change: Active	15.852	2.272	0.000	0.000
Total	6 weeks	Change: Placebo	−6.222	2.272	0.008	0.017

Table 2. Domain change score for participants on active treatment and placebo at week 3 and week 6

Variable	Time difference	Term	Estimate	SE	*p* value	Adjusted *p* value
SC subtotal	3 weeks	Interaction	−3.556	1.630	0.034	0.202
SC subtotal	3 weeks	Change: Active	2.630	1.152	0.027	0.186
SC subtotal	3 weeks	Change: Placebo	−0.926	1.152	0.425	0.866
SC subtotal	6 weeks	Interaction	−6.296	1.371	0.000	0.000
SC subtotal	6 weeks	Change: Active	3.815	0.969	0.000	0.003
SC subtotal	6 weeks	Change: Placebo	−2.481	0.969	0.013	0.134
SA subtotal	3 weeks	Interaction	−3.111	0.952	0.002	0.021
SA subtotal	3 weeks	Change: Active	3.259	0.673	0.000	0.000
SA subtotal	3 weeks	Change: Placebo	0.148	0.673	0.827	0.866
SA subtotal	6 weeks	Interaction	−6.296	1.124	0.000	0.000
SA subtotal	6 weeks	Change: Active	5.000	0.795	0.000	0.000
SA subtotal	6 weeks	Change: Placebo	−1.296	0.795	0.109	0.545
SB subtotal	3 weeks	Interaction	−4.481	0.863	0.000	0.000
SB subtotal	3 weeks	Change: Active	2.926	0.610	0.000	0.000
SB subtotal	3 weeks	Change: Placebo	−1.556	0.610	0.014	0.134
SB subtotal	6 weeks	Interaction	−5.370	1.002	0.000	0.000
SB subtotal	6 weeks	Change: Active	3.593	0.709	0.000	0.000
SB subtotal	6 weeks	Change: Placebo	−1.778	0.709	0.015	0.134
SO subtotal	3 weeks	Interaction	−2.704	0.724	0.000	0.006
O subtotal	3 weeks	Change: Active	2.074	0.512	0.000	0.002
O subtotal	3 weeks	Change: Placebo	−0.630	0.512	0.224	0.866
O subtotal	6 weeks	Interaction	−4.111	0.754	0.000	0.000
O subtotal	6 weeks	Change: Active	3.444	0.533	0.000	0.000
O subtotal	6 weeks	Change: Placebo	−0.667	0.533	0.217	0.866

in change from baseline between active treatment and placebo subjects.

For all four domains there are statistically significant increases for active treatment subjects at the week 6 time-point. For the sexual arousal (SA) domain, sexual behaviour (SB) and orgasm (O) domains there were also statistically significant changes and interactions at the week 3 time point. There were no statistically significant changes in the placebo group in any domains. These results are shown in Table 3.

It is noteworthy that positive changes were observed in the majority of the individual questions in the sexual arousal domain, relating to the ability to obtain full erections (Q6, Q7 and Q9). Similarly, all questions in the orgasm domain relating to ability, intensity and duration of orgasm (Q17, Q18, Q19 and Q21) were statistically significant.

Based on these results, there is evidence of improvement in libido, particularly in the physiological areas of sexual function and performance following treatment. As expected, changes are much more pronounced in the domains and Total DISF-SR than the individual questions.

General Quality of Life: The participants additionally completed a 5 point Likert scale of improvement at completion of the trial. These results indicate that majority of the active group felt improvements in libido (81.5%; 22 of 27), recovery time (66.7%; 18 of 27) and quality of sexual performance (63.0%; 17 of 27) as a result of receiving the active treatment. In addition, the majority of active treatment subjects also felt there was improvement in general energy (81.5%; 22 of 27) and wellbeing (55.6%; 15 of 27). Overall, there was very little change in mood and sleep in either the active treatment or the placebo group. There was no improvement in any of the questions in the placebo group. These results support the findings of the DISF-SR.

Analysis of Change in Hormone Levels: The FBC, PSA, total testosterone and prolactin levels were tested pre-test and the results were within normal reference range for all participants. The average serum testosterone levels were similar for both groups: active treatment group, 14.8 nmol/L (±6.3), placebo group, 14.6 nmol/L (±5.6). The serum testosterone levels remained within normal reference range after treatment

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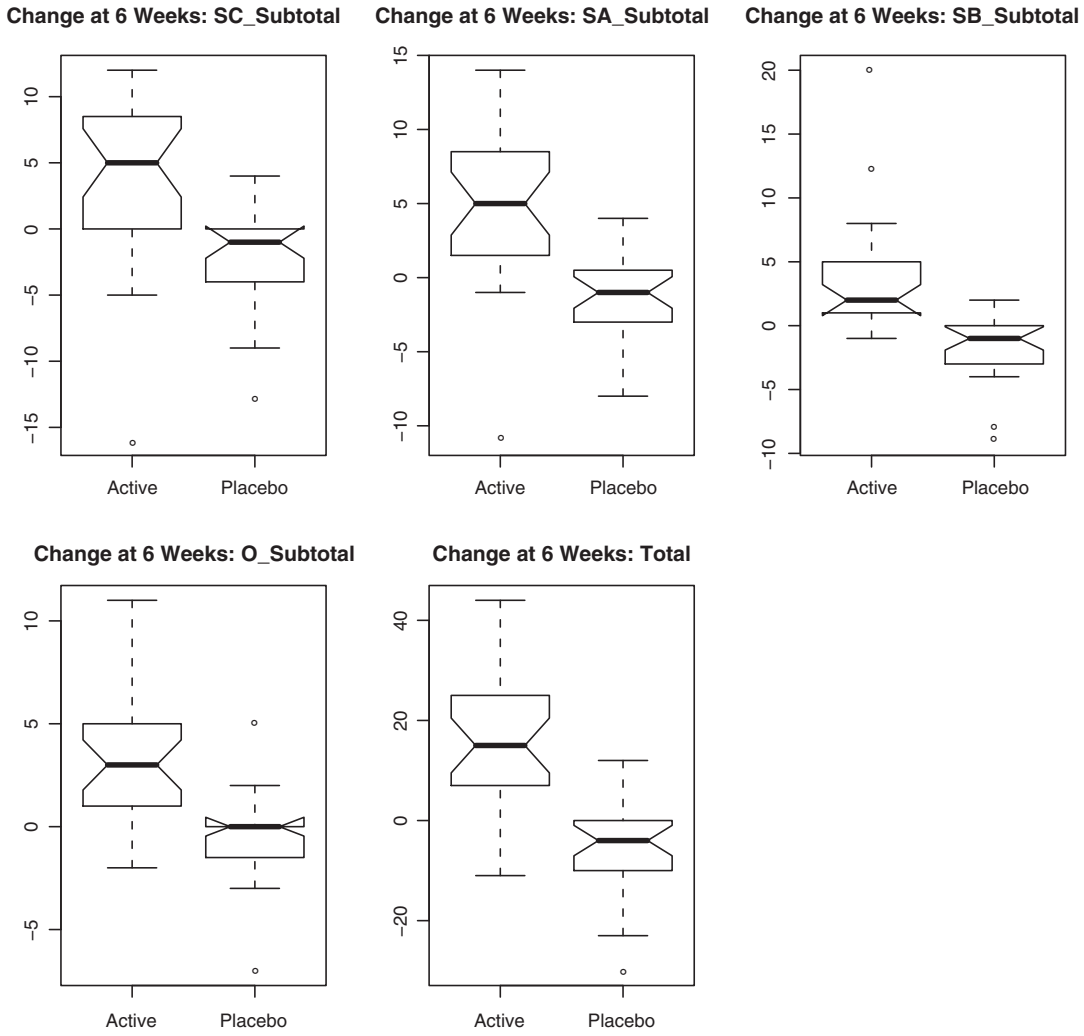

Figure 2. Changes from baseline for Domain Scores for participants on active treatment and placebo at week 6.

Table 3. DISF-SR domain sub-scores in the active and placebo groups at baseline, 3 and 6 weeks

Domains Average scores	Active group ($n = 27$)	Placebo group ($n = 27$)
1. Sexual cognition		
Baseline	21.78	23.96
Week 3	23.48	23.28
Week 6	25.36	21.68
Total possible score 40		
2. Sexual arousal		
Baseline	16.07	17.81
Week 3	18.70	18.16
Week 6	20.56	16.56
Total possible score 40		
3. Sexual behaviour		
Baseline	14.69	15.96
Week 3	17.29	14.53
Week 6	18.32	14.28
Total possible score 40		
4. Orgasm		
Baseline	14.78	15.18
Week 3	16.19	14.28
Week 6	18.24	14.29
Total possible score 24		

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in both the active treatment group (14.3 nmol/L (±5.8) and placebo group 13.1 nmol/L (±5.7). The average prolactin levels were similar for both groups: active treatment group, 5.8 μg/L (±1.8), placebo group, 6.0 μg/L (±2.6). There were no significant changes in prolactin levels after 6 weeks of treatment in either the active treatment group 6.3 μg/L (±1.7) or placebo group 6.0 μg/L (±2.6). There were no correlations between the different parameters of the study, i.e. age/serum testosterone, serum testosterone/ DISF-SR total score, age/DISF-SR total score.

Adverse events

There were no adverse events recorded during the clinical trial. The product was well tolerated, however, three of the participants in the active treatment group reported a slight stomach discomfort when taking it in the absence of food.

Summary

This study has demonstrated that there was a significant improvement in sexual function and performance following treatment with the active treatment. Additionally, there was a small reduction in performance for people treated with the placebo. The treatment did not affect testosterone or prolactin levels in this male sample study group at either 3 or 6 weeks.

DISCUSSION

This clinical trial has demonstrated that *Trigonella foenum-graecum* extract powder was efficacious in enhancing male libido in healthy adult males with normal testosterone, prolactin and PSA levels. In particular, positive changes were observed in the physiological aspects of libido. This was accompanied by improved quality of life, including well-being and energy. Also this study has shown that sexual satisfaction was associated with better quality of life.

Traditionally, *Trigonella foenum-graecum* has been reported to be useful in hormonal regulation, in particular for male impotence and as a galactagogue in lactating mothers (Zuppa *et al.*, 2010). Clinical studies, however, have focused primarily on the use of *Trigonella foenum-graecum* in the control of blood sugar and serum cholesterol levels. In 1990, Sharma and coauthors demonstrated that *Trigonella foenum-graecum* significantly reduced fasting blood sugar and serum total cholesterol, LDL and VLDL cholesterol and triglycerides. In 2008, Lu and coauthors conducted a larger trial on 69 type 2 diabetes mellitus patients taking hypoglycaemic drugs. They observed statistically significant decreases in FBG, 2h PBG, HbA1c and CSQS in the treated group compared with those in the control group (Lu *et al.*, 2008). More recently, a placebo-controlled parallel trial study of 39 overweight males demonstrated that a significant decrease in the insulin/glucose ratio and daily fat consumption, in overweight subjects administered the *Trigonella foenum-graecum* seed extract (Chevassus *et al.*, 2010). In a recent UK study of men with erectile dysfunction, it was identified that 82% were overweight or obese and 40% had metabolic syndrome (based on three or more of five criteria: waist circumference, high triglycerides, low levels of high-density lipoprotein cholesterol, hypertension and impaired glucose tolerance) (Somani *et al.*, 2010). It is noteworthy that the men in the present study, while being otherwise healthy were in the overweight category.

It is likely the saponins are, at least partly, responsible for these physiological effects. Petit *et al.* (1995) purified steroidal saponins from the *Trigonella foenum-graecum* seed extract and demonstrated a modification of the circadian rhythm of feeding behaviour, stabilization of food consumption and decreased total plasma cholesterol in diabetic rats. Further studies, looking at mechanisms of action, demonstrated that the hypolipidaemic effect was mediated through inhibition of fat accumulation and up-regulation of LDL receptor (Vijayakumar *et al.*, 2008). The mechanisms may be quite complex, as it was been further shown that the saponin 'diosgenin' present in fenugreek improves glucose metabolism by promoting adipocyte differentiation and inhibiting inflammation in adipose tissues (Uemura *et al.*, 2010). Shim *et al.* (2008) have shed further light on possible mechanisms of action of the saponins in *Trigonella foenum-graecum* seed extract. By using bioassay-guided fractionation, the authors identified steroidal saponins: gitogenin-O-beta-D-xylopyranosyl-(1-->6)-beta-D-glucopyranoside and dioscin that stimulate rat GH release in rat pituitary cells. While all of these are observations in cell and animal models, it has been established that there is a direct correlation between growth hormone, testosterone levels and age-related decline in both male and female libido.

A role for *Trigonella foenum-graecum* in supporting hormone mediated activity pathways has been shown previously in an unpublished double-blind randomized study, by Gencor Pacific, of 38 sedentary men who participated in a daily active exercise programme for 6 weeks. At the end of the programme, there was a significant increase in muscle mass, energy and stamina and an associated increase in serum testosterone levels. Similarly, the present study involved mainly sedentary men that were not involved in exercise, and supplementation with *Trigonella foenum-graecum* did not show changes in serum testosterone levels. It is possible that *Trigonella foenum-graecum* is metabolized differently when combined with exercise, or that a number of inter-related mechanisms of action are occurring.

Taken together, this research indicates that *Trigonella foenum-graecum* has potential in balancing hormones and, in particular, is a well tolerated naturally derived product to use to support libido in healthy males.

Conflict of Interest

The authors have declared that there is no conflict of interest.

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