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Influence of a Specialized *Trigonella foenum-graecum* Seed Extract (Libifem), on Testosterone, Estradiol and Sexual Function in Healthy Menstruating Women, a Randomised Placebo Controlled Study

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The aim of the study was to evaluate the effect of *Trigonella foenum-graecum* (fenugreek) seed extract on sex hormones and sexual function in healthy menstruating women who reported low sexual drive. This short term, single site, double blind, randomised, placebo-controlled study was conducted on 80 women, aged 20 to 49 years. Participants were randomised to either an oral dose of a standardised *T. foenum-graecum* seed extract (libifem) at a dose of 600 mg/day or placebo over two menstrual cycles. Dehydroepiandrosterone sulfate, progesterone, androstenedione, total and free testosterone, estradiol (E2), luteinizing hormone, follicle stimulating hormone, sex hormone binding globulin and cholesterol were measured at baseline and 8 weeks. The individual aspects of sexual function were measured using the Derogatis interview for sexual functioning and female sexual function index self-administered questionnaires. Stress, fatigue and quality of the relationship with partner were also measured using the PSS (Perceived Stress Scale), MFI-20 (Multidimensional Fatigue Inventory) and DAS (Dyadic Adjustment Scale) quality of life measures, respectively. There was a significant increase in free testosterone and E2 in the active group as well as sexual desire and arousal compared with the placebo group. The results indicate that this extract of *T. foenum-graecum* may be a useful treatment for increasing sexual arousal and desire in women. **Copyright © 2015 John Wiley & Sons, Ltd.**

Keywords: Trigonella foenum-graecum; fenugreek; oestrogen; estradiol; testosterone; sexual desire; sexual function.

INTRODUCTION

Sexual functioning involves a complex set of interactions between sex hormones [estradiol (E2) and testosterone], the autonomic nervous system and environmental factors (e.g. mental health, fatigue and quality of life) (Basson, 2006). Estrogens and androgens play an important role in stimulating sexual desire and arousal (Simon, 2011; Riley and Riley, 2000). Estradiol stimulates vaginal lubrication and blood flow, affecting a woman's capacity for sexual arousal and orgasm (Simon, 2011), and free testosterone is linked with sexual desire.

Thirty-nine percent of younger pre-menopausal women report low sexual desire (West *et al.,* 2008). The Women's International Study of Health and Sexuality reported decreased sexual functioning was associated with significant emotional and psychological distress, as well as lower sexual and relationship satisfaction (Leiblum *et al.,* 2006).

Ageing and a concomitant reduction in endogenous androgen levels are associated with a parallel decline in sexual function (Davison *et al.,* 2005). The pathophysiology that defines androgen insufficiency in pre-menopausal women is underpinned by a decrease in testosterone whilst maintaining normal E2 levels. Clinical symptoms include decreased libido, reduced sexual receptivity and pleasure, a diminished sense of well-being, dysphoric mood and/or reduced motivation and persistent unexplained fatigue (Yasui *et al.,* 2012). Santoro *et al.* (2005) reported that endogenous testosterone levels were minimally associated with higher sexual desire in women aged 42–52 years. Conversely, there is a positive correlation between low testosterone levels and decreased libido in pre-menopausal women (Riley and Riley, 2000; Guay, 2001).

Transdermal testosterone has been shown to increase sexual desire in postmenopausal women (Hobbs and Handler, 2013). However, testosterone supplementation may be associated with thrombosis in women, and long-term safety has not been established (Glueck *et al.,* 2013).

Trigonella foenum-graecum is of interest as a potential therapy for improving sexual function as it is a botanical extract rich in steroidal saponins reported to exhibit estrogenic effects including binding to E2 receptors and inducing the expression of E2 responsive genes (Sreeja *et al.,* 2010). It has also been shown in previous studies to increase sexual function in men (Steels *et al.*, 2010).

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AIMS

The aim of this clinical trial was to firstly document the relationship between sexual function and circulating hormones (i.e. free testosterone and E2), in healthy menstruating women with low sexual function. The resultant hypothesis was that low sexual function in healthy menstruating women is associated with deficits in circulating testosterone and E2. Secondly, the other aim is to investigate the efficacy and safety of *T. foenum-graecum* seed extract, in improving individual aspects of sexual functioning and to document any hormonal changes with a concomitant beneficial shift in circulating sex hormone levels.

METHODS

This study was a single site, randomised, double blinded clinical trial that recruited 80 healthy menstruating women, with a 1:1 allocation ratio to either active ($n=40$) or placebo ($n=40$) (Fig. 1). The study was carried out according to the principles expressed in the declaration of Helsinki and was approved by the Queensland Clinical Trial Network Human Research Ethics Committee number 2011001. The clinical trial was registered with the Australia New Zealand Clinical Trial Registry number 12611001031954.

The participants were healthy menstruating women with regular menstrual cycles (between 28–34 days), between 20–49 years of age, with no diagnosed chronic diseases or prescribed pharmaceutical medications for chronic disease, body mass index (BMI) <35, blood pressure <130/90 and normal fasting blood glucose levels. All participants reported low sexual desire and were in a sexual relationship. All women were on the contraceptive pill or were using other forms of contraception (including barrier method) to prevent pregnancy. Potential participants were excluded if they had received androgen therapy within 3 months of recruitment, were pregnant or attempting to conceive and had been breastfeeding within 3 months prior to the study. They were ineligible if they had experienced any chronic or acute life stressors relating to a major life change, were experiencing depression and/or receiving medication for such illness or disorders, were receiving statins or other drugs known to impact on steroid hormone levels, had a serious illness, active gall bladder disease, gynaecological or breast surgery within the last 6 months, had a history of breast, endometrial, or other gynaecological cancer at any time before study participation or other cancer within the last 5 years, were on medication for diabetes and had a history of cerebrovascular disease, thrombo-embolic disorders, heart attack, or angina at any time before study participation or thrombophlebitis within the last 5 years. In addition, women who were taking anti-coagulant or anti-platelet drugs on a daily basis for any conditions were excluded.

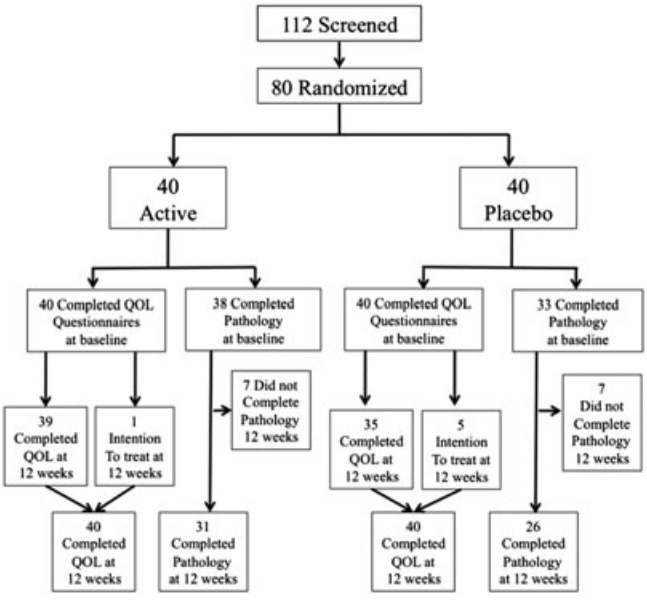

Figure 1. Flowchart of subject participation in trial.

Potential participants were recruited from databases and public media outlets in Brisbane, Australia, from November 2011 to September 2012. They were screened initially via online questionnaires, followed by a telephone call, prior to an initial baseline interview, at which time each participant completed the consent form. At the baseline interview, a medical history, a medical assessment and questionnaires were completed. Participants completed a fasting blood test during the follicular phase of their next menstrual cycle on the morning of day 7 to 9. Participants were given the investigational product with instructions to commence the treatment after the initial blood test. At month 1, participants completed the libido questionnaire (Derogatis interview for sexual functioning, DISF-SR). At month 2 (on day 7 to 9), participants repeated the fasting blood test. Within 1 week of completion of the trial, a trial-exit interview was conducted, and the questionnaires were completed again. Participants were monitored for compliance with the protocol by a combination of telephone and email communications and the return of bottles and unused product at completion of the trial.

The investigational product contained 300 mg of libifem, a standardised extract of *T. foenum-graecum* (fenugreek) seed extract [dry concentrate 33:1, equivalent to 9.9 g dry herb, standardised to a minimum 50% saponin glycosides (Fig. 2)] supplied by Gencor Pacific Ltd. and 30 mg of the flow agent maltodextrin, in a two-piece white hard gelatin non-marked capsule size 0. The placebo product contained 330 mg maltodextrin, also in a size 0 non-marked, hard gelatin capsule. Libifem and placebo capsules were administered as two capsules per day with food, one before breakfast and one before dinner, for two menstrual cycles.

The randomization of participants to active treatment or placebo was conducted independently to the investigators, using random allocation software.

Sample size and statistical analysis – a minimum number of 33 participants per group were required to achieve a statistical power of 80% on the basis of a 20% increase in average sexual function as measured by the total domain score of the DISF-SR. The DISF-SR total score and the individual domain scores were analysed for significance using the non-parametric Wilcoxon signed rank test. The female sexual function index (FSFI) and pathology data were analysed for significance using independent sample *t*-tests. The correlations were analysed using the Pearson correlation coefficient.

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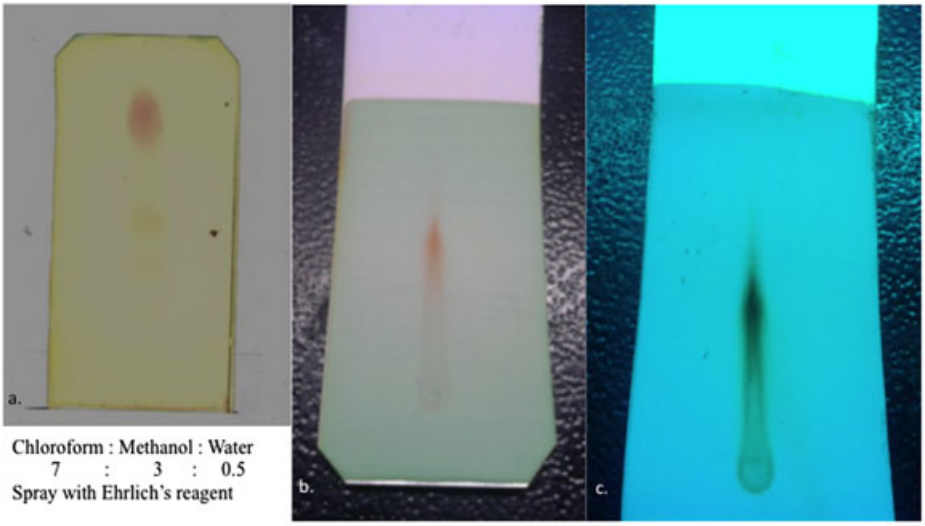

Figure 2. TLC (Thin Layer Chromatography) identification of furostanol saponins in *Trigonella foenum-graceum* (libifem extract). (a) Standard with Ehrlich's reagent, (b) libifem with Ehrlich's reagent and (c) methapolic sulfuric and reagent Schwarz, M. W. 2000, saponins, Ullmann's Encyclopedia of Industrial Chemistry. This figure is available in colour online at wileyonlinelibrary.com/journal/ptr.

MAIN OUTCOME MEASURES

Metabolism and sex hormones

The following tests were measured at baseline and month 2: weight, BMI, FBC (Full Blood Count), electrolyte/liver function, cholesterol, testosterone, sex hormone binding globulin (SHBG), E2, androstenedione, dehydroepiandrosterone sulfate (DHEA-S), follicle stimulating hormone (FSH), luteinizing hormone (LH), progesterone and prolactin. Free testosterone was calculated using testosterone and SHBG data as per the Sodergard equation (Sodergard *et al.,* 1982). The hormone data were further analysed excluding those on the oral contraceptive pill (OCP) and to evaluate change scores (difference between baseline and month 2).

Sexual function

Sexual function was evaluated using the FSFI and the DISF-SR. The FSFI is a 19-item questionnaire divided into six domains: desire, arousal, lubrication, orgasm, satisfaction and pain (Rosen *et al.,* 2000; Meston, 2003). The differentiation point for sexual dysfunction was defined as a score of <26 (Wiegel *et al.,* 2005).

Table 1. Participant demographics

	Total (n = 80)	Placebo (n = 40)	Active (n = 40)
Age	–	–	–
Mean (SD)	34.9 (7.9)	34.9 (8.3)	34.9 (7.6)
Range	20–49	22–49	20–49
Height (m) (SD)	1.67 (6.6)	1.67 (6.3)	1.67 (6.7)
Weight (kg) (SD)	69.4 (16.1)	68.7 (16.8)	69.5 (15.0)
Body mass index (BMI) (SD)	24.9 (5.5)	24.9 (6.0)	24.8 (5.0)
Number of children	–	–	–
Mean	1.1	0.9	1.1
Range	0–4	0–3	0–4
Smoking	–	–	–
No (number, %)	74/80 (92.5%)	38/40 (95%)	36/40 (90%)
Yes (number, %)	6/80 (7.5%)	2/40 (5%)	4/40 (10%)
Alcohol intake	–	–	–
No (number, %)	22/80 (27.5%)	8/40 (20%)	14/40 (35%)
Social (number, %)	58/80 (72.5%)	32/40 (80%)	26/40 (65%)
Exercise patterns	–	–	–
None (number, %)	14/80 (17.5%)	7/40 (17.5%)	7/40 (17.5%)
Regular (number, %)	66/80 (82.5%)	33/40 (82.5%)	33/40 (82.5%)
Oral contraceptive pill (OCP)	–	–	–
Yes (number, %)	26/80 (32.5%)	15 (37.5%)	11 (27.5%)
No (number, %)	54/80 (67.5%)	25 (62.5%)	29 (72.5%)

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Table 2. Mean (SD) hormone levels before and after intervention in active treatment and placebo groups

	Total	Placebo		Active		
Pathology	Baseline (n = 71)	Baseline (n = 33)	Month 2 (n = 26)	Baseline (n = 38)	Month 2 (n = 31)	Change from baseline to month 2, active versus placebo p value
Cholesterol (mmol/L) healthy reference range 3.6–6.7	4.93 (0.75)	5.34 (0.75)	5.07 (0.73)	5.10 (0.84)	4.88 (0.79)	0.683
Androstenedione (nmol/L) healthy reference range 1.1–11.5	6.39 (3.53)	7.21 (4.15)	7.30 (3.98)	5.66 (2.74)	6.65 (3.92)	0.078
Dehydroepiandrosterone (DHEA)-sulfate (μmol/L) healthy reference range (1.4–11.7)	4.02 (1.72)	4.35 (1.96)	4.46 (1.95)	3.74 (1.44)	3.81 (1.41)	0.747
Prolactin (μg/L) healthy reference range $<$20	11.25 (7.96)	10.78 (7.91)	12.04 (11.5)	11.65 (8.10)	12.41 (6.95)	0.323
Luteinising hormone (U/L) healthy reference range 4–30	10.91 (8.84)	12.85 (11.22)	12.36 (9.53)	9.19 (5.60)	13.00 (12.54)	0.179
Follicle stimulating hormone (FSH) (U/L) healthy reference range 3–20	16.31 (12.95)	18.58 (14.68)	21.47 (28.41)	14.30 (10.10)	12.77 (8.67)	0.416
Progesterone (nmol/L) healthy reference range $<$5	1.33 (0.63)	1.29 (0.70)	1.35 (0.87)	1.37 (0.55)	1.30 (0.54)	0.692
Estradiol (pmol/L) non-OCP group * healthy reference range 70–530	260.5 (192.6)	284.19 (201.3)	286.88 (239.6)	242.71 (187.5)	403.0 (333.0)	0.013
Testosterone (nmol/L) non-OCP group * healthy reference range 0.3–2.8	1.09 (0.53)	1.22 (0.54)	1.39 (0.55)	1.00 (0.49)	1.17 (0.53)	0.478
Free testosterone (pmol/L) non-OCP group* healthy reference range 0.2–13	1.43 (0.81)	1.82 (0.83)	1.72 (0.67)	1.13 (0.66)	1.40 (0.69)	0.043
Sex hormone binding globulin (nmol/L) non-OCP group* healthy reference range 18–144	60.35 (24.42)	56.19 (24.00)	61.44 (26.20)	63.52 (24.08)	62.86 (19.89)	0.132

*Non-OCP group, placebo (baseline n = 21, month 2 n = 16) and active (baseline n = 28, month 2 n = 23).
OCP, oral contraceptive pill.

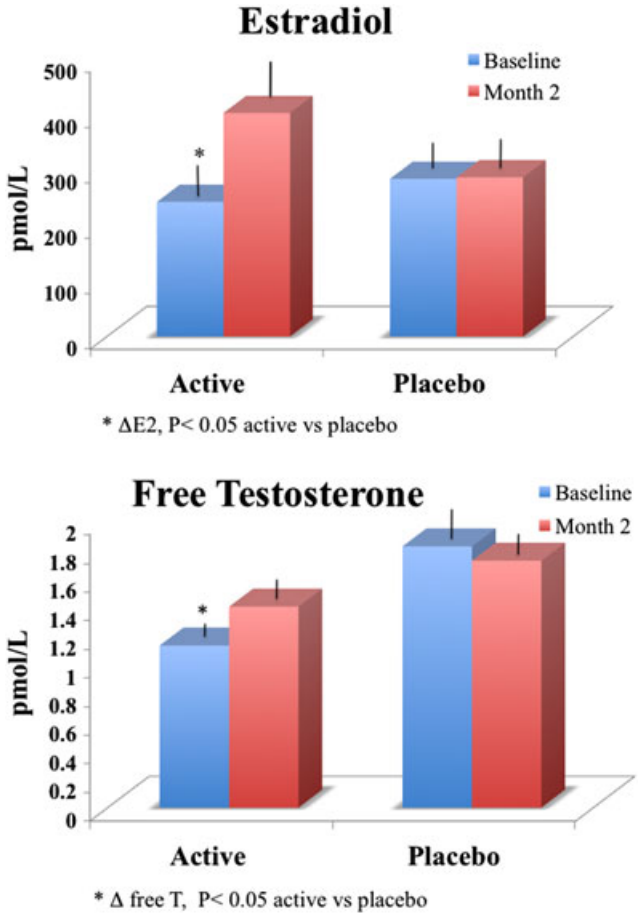

Figure 3. (A and B) Estradiol and free testosterone levels at baseline and month 2 in the active treatment and placebo group (non-OCP users). * ΔE2, $p < 0.05$ active versus placebo and * Δ free T, $p < 0.05$ active versus placebo. This figure is available in colour online at wileyonlinelibrary.com/journal/ptr.

The DISF-SR is a brief semi structured interview designed to provide the quality of an individual's current sexual functioning in quantitative terms. The DISF-SR represents quality of current sexual functioning in a multi-domain format, which parallels the phases of the sexual response cycle (Masters and Johnson, 1966; Derogatis and Mellisaratos, 1979; Basson *et al.,* 2000). The 25 interview items of the DISF-SR are arranged into five domains of sexual functioning: I. sexual cognition /fantasy, II. sexual arousal, III. sexual behaviour/experience, IV. orgasm, V. sexual drive/relationship. The change from baseline to month 2 was calculated for each of the sexual function questionnaires and was compared between the active treatment and placebo groups.

Stress, fatigue and relationship quality

The perceived stress scale (PSS) was used to assess stress. It is a measure of the degree to which situations in one's life are appraised as stressful. Items were designed to tap how unpredictable, uncontrollable and overloaded respondents find their lives (Cohen *et al.,* 1983). The multi-dimensional fatigue symptom inventory (MFI-20) was used to assess fatigue. The MFI-20 provides a total score for fatigue and also includes the individual domains of general, emotional, physical, mental health and vigour as separate aspects to fatigue (Stein *et al.,* 1998). The dyadic adjustment scale (DAS) is a 32-item measure of relationship quality with their partner (Spanier, 1976).

Safety

Safety and tolerability were determined by recording menstrual cycle pattern and adverse events, and biochemically by measuring full blood count, renal and liver function serum, sex hormone levels, glucose and cholesterol.

RESULTS

Participant demographics

The active treatment and placebo groups were well matched for age, active treatment group 34.9 ± 7.6 years and placebo group 34.9 ± 8.3 years. The average BMI for both groups was also similar, (active treatment group 24.8 ± 5.0 kg/m^2 and placebo group 24.9 ± 6.0 kg/m^2) and was considered in the normal healthy weight range. The majority of women in both groups was non-smokers (active treatment group, 90% and placebo group, 95%), classified themselves as social drinkers (65% active treatment group and 80% placebo group) and reported undertaking regular exercise (82.5%) (Table 1).

In this study group, all women were considered healthy by definition of full blood count, fasting cholesterol, fasting glucose, liver and kidney function, prolactin and regular menstrual cycles being within normal healthy range. All women were using a form of contraception, either OCP (active treatment group, 11/40 and placebo group, 15/40) or barrier methods (active

Table 3. Sexual function, as measured by Derogatis interview for sexual functioning (DISF-SR), at baseline and month 2 in active treatment and placebo group (mean, SD)

	Placebo		Active		
	Baseline	Month 2	Baseline	Month 2	Change from baseline to month 2, active versus placebo p value
Sexual cognition	14.5 (8.29)	14.58 (7.84)	13.15 (8.81)	16.45 (9.60)	0.013
Sexual arousal	12.66 (4.92)	12.15 (5.78)	11.58 (6.34)	15.28 (7.14)	0.0001
Sexual behaviour/experience	11.85 (5.09)	12.58 (6.22)	10.88 (5.21)	14.11 (6.29)	0.006
Orgasm	12.63 (5.55)	12.78 (6.11)	10.63 (5.45)	13.28 (6.17)	0.001
Sexual drive/relationship	11.80 (3.82)	12.65 (3.95)	11.58 (4.26)	13.86 (4.70)	0.048
Total	63.56 (20.12)	65.06 (23.30)	57.80 (25.74)	72.98 (30.56)	0.001

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treatment group, 29/40 and placebo group, 25/40). The menstrual pain scores were similar in both groups. The majority of women completed the baseline hormone profiles (active treatment group, $n=38$ and placebo group, $n=33$). The menstrual cycle hormones (LH, FSH and E2) were within the reference range for the follicular phase of the menstrual cycle for all participants. The total testosterone levels ranged from 0.1–2.5 nmol/l (reference range 0.3–2.8 nmol/l). Of these, five (5/71) were below 0.1 nmol/l, 22 (22/71) in the lower 25%, 35 (35/71) between 25–50% and only eight (8/71) over 50% of the reference range. The free testosterone levels were lower than the 50% of reference range for all but one participant (70/71).

There was no statistically significant difference between the hormone levels or measures of sexual functioning (using total and domain scores of the FSFI and DISF-SR) between the active treatment group and placebo groups at baseline. The quality of the participants' relationship with their partner was rated as high in both groups as measured by the DAS (active treatment group, score of 104.4/151 and score of placebo group, 102.2/151). There was no significant difference between the groups in perceived stress levels (measured by the PSI) or fatigue scores (measured by the MFSI).

Age was positively correlated with weight, BMI and parity. Age was negatively correlated with DHEA-S ($r=-0.40$ and $p=0.001$), androstenedione ($r=-0.30$ and $p=0.013$) and SHBG ($r=-0.33$ and $p=0.005$) as well as sexual function (total DISF-SR) ($r=-0.46$ and $p=0.001$) and arousal (DISF-SR sub-domain II) ($r=-0.34$ and $p=0.002$). There was no correlation between age and total testosterone or free testosterone. There was a positive correlation between age and E2 in non-OCP users ($r=0.32$ and $p=0.013$). Baseline total testosterone and free testosterone positively correlated with the domain of sexual drive/relationship (DISF-SR IV) ($r=0.360$ and $p=0.006$) ($r=0.348$ and $r=0.007$). Total testosterone also demonstrated a positive correlation with the domain of orgasm (DISF-SR V) ($r=0.265$ and $p=0.033$). There was no any correlation between baseline levels of E2 and indices of sexual function.

Effect of *Trigonella foenum-graecum* seed extract on metabolism, sex hormones and sexual function

Body weight did not change for either group over the study period. There were no changes in FBC, liver function tests and triglyceride levels in either group following treatment. Total cholesterol, DHEA-S, androstenedione and prolactin were similar at baseline and at month 2 for both active treatment and placebo groups. The results obtained for the sex hormones were analysed for the whole cohort and separately for non-OCP users in both the active treatment and placebo groups. There was a significant inter-group difference in the change in hormone concentration between baseline and month 2 for calculated free testosterone ($p=0.043$) and E2 ($p=0.013$) comparing the active and placebo treatment groups, (Table 2, Fig. 3).

There was a significant inter-group difference in the mean change of score of the FSFI sexual arousal domain from baseline to month 2 comparing the active treatment and placebo ($p=0.026$). The total and other individual domains of the FSFI did not show significant inter-group differences. There was a significant inter-group difference in the change from baseline in all domains and the total score of the DISF-SR (Table 3). There was no significant difference in the results of the DISF or FSI questionnaires between the OCP and non-OCP users.

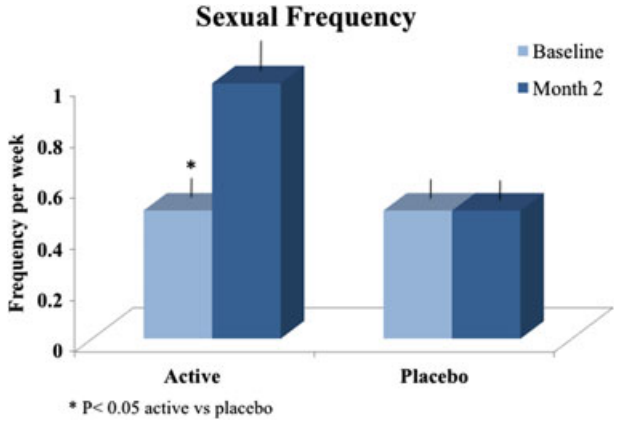

Figure 4. Frequency of sexual activity at baseline and month 2 in the active treatment group and placebo group. * Δ sexual frequency, $p<0.05$ active versus placebo. This figure is available in colour online at wileyonlinelibrary.com/journal/ptr.

The frequency of sexual activity was assessed using DISF-SR question 3.5 'During the past 30 days, or since the last time you filled out this inventory, how often did you engage in sexual intercourse, oral sex, etc.'. The frequency in active treatment group increased from 1–2 times per month to once per week. The frequency of sexual activity in the placebo group remained the same at month 2, at 1–2 times per month. The change in sexual frequency from baseline to month 2 was significantly different between the active treatment and placebo group ($p=0.013$) (Fig. 4).

There were no changes in the quality of relationship in either group.

Adverse reactions

There were no major adverse reactions reported. However, there were minor reactions, exacerbation of migraines ($n=2$) and indigestion/reflux ($n=2$) in the active treatment group. No reactions were reported in the placebo group.

DISCUSSION

The results of this clinical trial have demonstrated that the specialized extract of *T. foenum-graecum* seed extract (libifem) has a positive effect in enhancing sexual function in healthy menstruating women with self-reported low sexual function. In particular, positive changes were observed in both sexual desire and arousal. Furthermore, *T. foenum-graecum* significantly increased levels of E2 and calculated free testosterone compared to placebo. The botanical extract did not have an effect on cholesterol, LH or FSH levels, other hormones or the length or characteristics of each menstrual cycle.

The majority of women in the study had baseline-free testosterone levels in the lower half of the healthy

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reference range. There were significant positive correlations between sexual desire and both free and total testosterone. Although, there have been studies on pre-menopausal women suggesting a correlation between sexual desire and free testosterone, more recent studies have show that the relationship is difficult to establish (Basson *et al.*, 2010; Davis *et al.,* 2005; Dennerstein *et al.,* 2005). Nevertheless, given that pharmacological doses of testosterone improve sexual function in women (Pluchino *et al.,* 2013), the finding that *T. foenum-graecum* increases free testosterone may be one potential mechanism of its effect.

Administration of *T. foenum-graecum* seed extract was also associated with a significant increase in E2 levels. Estradiol stimulates vaginal lubrication and blood flow, affecting a woman's capacity for sexual arousal and orgasm (Simon, 2011); this supports the significant positive change in sexual arousal observed. Whilst the mechanism of the increase in E2 levels is unclear from the current study, one possibility is due to increased aromatase activity that converts testosterone to E2.

There have been no other studies on the effect of *T. foenum-graecum* on female sexual function. However, the results are supported by previous research undertaken on this botanical extract in men that reported increased sexual function and energy levels in sedentary men (Steels *et al.,* 2011). Further studies are required to establish the specific mechanism of action.

The placebo response was robust as is expected as when women want their sexual lives to be improved (Braunstein *et al.,* 2005). This may explain why women in both groups reported an increased satisfaction with their relationship at the end of the study, but nevertheless, there remained a significant treatment effect from the *T. foenum-graecum* seed extract.

A limitation of the study was that not all participants (for various reasons) underwent the follicular phase blood tests on days 7–9 of the trial, reducing the data available. This was more common in the placebo group at completion. The also trial included women using the OCP that limited the analysis of E2, free testosterone and SHBG to the non-OCP users. However, all sexual function data were analysed, and results indicated that the herbal treatment was effective in increasing sexual function in both the OCP and non-OCP users. It is recommended that future studies be conducted over an extended periods of time to determine any longer term hormonal changes in larger cohorts of women.

This study has provided further evidence that *T. foenum-graecum* seed extract is a well tolerated and is an effective botanical medicine for use in the support of sexual function of pre-menopausal women, in particular increasing sexual desire and arousal, with positive effects on concentrations of E2 and free testosterone.

AUTHOR CONTRIBUTIONS

Conducted clinical trial recruitment, A. R. and E. S.. Participant assessments, A. R. and E.S.. Analysed the data, A. R., G. B. and L.V.. Wrote the manuscript, A. R., E. S., G. B. and L. V.. Critically reviewed the manuscript, A. R., E. S., G. B., W. I. and L. V..

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DISCLOSURES

Luis Vitetta has received National Institute of Complementary Medicine/National Health and Medical Research Council competitive funding and industry support for research into nutraceuticals and herbal medicines.

Conflict of Interest

Funding and study medication for the project was received from the clinical trial sponsor Gencor Pacific Pty. Ltd., Hong Kong. The sponsor had no involvement in the collection, analysis or interpretation of the data, writing the report or the decision to submit the paper for publication.

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