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Efficacy of a Proprietary *Trigonella foenum-graecum L.* De-Husked Seed Extract in Reducing Menopausal Symptoms in Otherwise Healthy Women: A Double-Blind, Randomized, Placebo-Controlled Study

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Trigonella foenum-graecum **seed extract has demonstrated hormone modulatory activity, providing biological plausibility for relieving menopausal symptoms. The study aimed to assess efficacy of a standardized *T. foenum-graecum* de-husked seed extract in reducing menopausal symptoms in healthy aging women. The study was a double-blind, randomized, placebo-controlled trial that recruited 115 women aged 40 to 65 years of which 59 were allocated to active (n = 54 completed) and 56 to placebo (n = 50 completed). Active treatment was *T. foenum-graecum* de-husked seed extract, 600 mg per day for 12 weeks. Outcome measures included Menopause-Specific Quality of Life (MENQOL) questionnaire, frequency of hot flushes and night sweats and serum estradiol levels. There was a significant reduction in menopausal symptoms in the active group compared with placebo as assessed by total MENQOL score ($p < 0.001$); reflected by significant improvements in the vasomotor ($p < 0.001$), psychosocial ($p < 0.001$), physical ($p < 0.001$) and sexual symptoms ($p < 0.001$) domains. Vasomotor outcomes correlated with hot flushes, the active group reporting significantly less daytime hot flushes and night sweats at 12 weeks ($p < 0.001$). The average estradiol levels were similar in both the active group and placebo group after treatment. This study demonstrated that this proprietary *T. foenum-graecum* de-husked seed extract may reduce menopausal symptoms in healthy women.**

Keywords: Trigonella foenum-graecum; fenugreek; menopause; hot flushes; night sweats.

INTRODUCTION

Menopause is the permanent cessation of menstruation and fertility resulting from the loss of ovarian follicular activity. Menopause is associated with vasomotor, physical and psychosocial symptoms as well as changes in sexual function. Both the nature and severity of symptoms vary substantially between women and generally occur between the ages of 40 and 58 years, and persist for a duration of 5 to 8 years (Roberts and Hickey, 2016). The most prominent changes are the vasomotor symptoms of hot flushes and night sweats, which can affect up to 80% of women. Over 50% of Western women use integrative medicines such as soy isoflavones, red clover and black cohosh to treat the symptoms of menopause, and their use is associated with a modest reduction in the frequency of symptoms (Franco *et al.*, 2016; Sarri *et al.*, 2017). Botanical therapies commonly used for menopausal symptoms such as soy isoflavones and red clover are classified as phytoestrogens or phytosterols in that they are compounds that bind to oestrogen receptors (Dean *et al.*, 2017). Most of the clinical research has focused on the use of phytoestrogens as an alternative to hormone therapy for managing menopausal symptoms such as hot flushes (Rietjens *et al.*, 2016).

Trigonella foenum-graecum is a traditional herbal drug and spice that has been utilized since antiquity by many cultures for its pharmaceutical effects including anti-microbial, anti-lipidemic, hypocholesterolemic, antiinflammatory, hepatoprotective, hypoglycaemic and gastric stimulant activities (Yadav and Baquer, 2014; Khosla *et al.*, 1995; Sharma *et al.*, 1990; Pandian *et al.*, 2002). The seed of *T. foenum-graecum* contains active components such as amino acids, fatty acids, vitamins, saponins, dietary fibers (i.e. galactomannan), isoflavonoids, polysaccharide sugars (galactose and mannose), fixed oils and some alkaloids (trigonelline and choline) (Yadav and Baquer, 2014). Earlier research reported that *T. foenum-graecum seed* exhibits estrogenic (Aradhana *et al.*, 1992) and galactogogue activity (Tiran, 2003). Chloroform extracts of *T. foenum-graecum* seeds were also shown to bind to estradiol receptors and induce the expression of estradiol responsive genes (Sreeja *et al.*, 2010). Little is known, however, about the estrogenic effects of *T. foenum-graecum* (Yadav and Baquer, 2014). A recent

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study reported that a standardized extract of *T. foenum-graecum* seed extract, rich in saponins and de-husked (i.e. endosperm only), was associated with increased serum estradiol levels, improved sexual function and quality of life in healthy menstruating women (Rao *et al.*, 2015). An earlier study reviewed the effect of a *T. foenum-graecum* seed extract on hot flushes in menopausal women and suggested that the extract is safe and effective for reducing both the number and intensity of vasomotor symptoms (Alizadeh and Mehraban, 2012). Furthermore, Hakimi *et al.* (2006) in a non-blinded clinical study demonstrated that *T. foenum-graecum* seed powder was effective in reducing hot flushes associated with menopause. The authors concluded that *T. foenum-graecum* seed was associated with a decrease in the number of hot flushes experienced by women, but effectiveness was less than that reported with hormone therapy.

Most recently, a phytoestrogen rich *T. foenum-graecum* seed extract, consisting of the husk, was found to have a positive effect on menopausal symptoms such as hot flushes, night sweats and mood swings with an associated increase in estrogen (Begum *et al.*, 2016). These results suggest that there is a plausible rationale for the use of various *T. foenum-graecum* seed extracts as a phytoestrogen and/or hormone modulator for supporting estradiol levels during the menopause phase and reducing the associated symptoms. This study aimed to investigate the efficacy of a standardized proprietary *T. foenum-graecum* de-husked seed extract in reducing vasomotor symptoms and improving quality of life over 12-week duration in healthy women experiencing menopausal symptoms.

PARTICIPANTS AND METHODS

Study design. The study was a double blind, randomized, placebo-controlled clinical trial, conducted between November 2014 and March 2016 in Brisbane, QLD, Australia. The study protocol complied with the Helsinki Declaration and was approved by the University of Queensland Clinical Human Research Ethics Committee. The trial was registered with the Australian New Zealand Clinical Trials Registry (ANZCTR, Trial ID: ACTRN12615000324516) and with the TGA clinical trial notification (CTN) scheme.

Participant selection. The study cohort comprised of healthy women, 40 to 65 years of age who were experiencing menopausal symptoms including hot flushes, night sweats and other associated symptoms, and included women that were both peri-menopausal (having irregular menstrual cycles in last 12 months) and menopausal (cessation of menstruation). Participants were recruited through the contract research organizations (CROs) subject database and public media avenues. After preliminary screening via telephone, participants were required to attend a pre-trial interview and then provide informed consent. Comprehensive screening was performed after an initial health assessment including lifestyle questionnaires, current medication use, medical history and a physical examination.

The inclusion criteria were the presence of hot flushes and/or night sweats scoring greater than mild on the Menopause-Specific Quality of Life (MENQOL) questionnaire, and being able to adhere to protocol requirements. Potential participants were excluded if they had been using hormone therapies or herbal medicines for menopausal symptoms for at least 1 month prior to trial commencement. Women were also excluded if they had a previous history, presence or suspicion of estrogen-dependent neoplasia, neoplastic disease or treatment for any neoplastic disease within the previous 2 years; had a total hysterectomy; had active or a recent history (in the last 6 months) of thromboembolic disease; had a history of cerebrovascular accident, stroke or transient ischemia or had major depressive disorder, bipolar disorder, psychotic disorder or generalized anxiety disorder requiring therapy. Women that had uncontrolled diabetes, high cholesterol or hypertension, active substance abuse (alcohol or drug dependency) or experienced unintended weight loss of more than 15% of body weight in the last 6 months were also excluded. A body mass index (BMI) greater than 35, being vegetarian and/or consuming soy products regularly were further criteria for exclusion. The clinical trial excluded women that were currently using other investigational product(s).

Intervention. The investigational product was provided by Gencor Pacific, Hong Kong. It contained 300 mg of a proprietary extract of *T. foenum-graecum* de-husked seed extract, Libifem®, [dry concentrate 33:1, equivalent to 9.9-g dry herb, standardized for a minimum of 50% content of furostanol saponins] in a two-piece opaque, hard gelatin and non-marked capsule. Thin layer chromatography identification of furostanol saponins in this proprietary extract was reported by Rao *et al.* (2015). The placebo contained maltodextrin only, also in a two-piece opaque, hard gelatin and non-marked capsule. The investigational product and the placebo capsules were identical in appearance. Participants were randomly allocated (blinded) to the active or placebo group and were instructed to take 600 mg per/day (1 × 300 mg capsule b.i.d.) with food, at breakfast and with evening meals for 12-weeks duration. Participants were monitored for compliance by a combination of both telephone and email communications.

Randomization and blinding. Randomization was performed independently of the investigators using Random Allocation Software, version 1.0. The investigational products were provided to the investigators packaged in numbered identical white, opaque containers. Once enrolled into the trial, participants were given the next available numbered bottle. Participants were monitored for compliance during the study duration through telephone and email communications with the number of returned capsules assessed at completion of study to determine dosage adherence.

Objectives and outcomes

Primary outcomes. The primary outcome measure was efficacy of treatment for menopausal symptoms using the MENQOL questionnaire and also a 7-day diary of the number of hot flushes and night sweats

recorded by participants at baseline (prior to commencement), T_4, T_8 and T_{12} week time points. The MENQOL is a validated questionnaire assessing the impact of menopausal symptoms on health-related quality of life during the menopausal period (Hilditch *et al.*, 1996). The MENQOL is self-administered and has a total of 29 items in a Likert-scale format. It assesses four domains of menopausal symptoms as experienced over the last month to include: vasomotor (items 1–3); psychosocial (items 4–10); physical (items 11–26) and sexual (items 27–29). Items are rated as present or not present, and if present how bothersome on a zero (not bothersome) to six (extremely bothersome) scale. Participants were asked to record a 7-day period of vasomotor episodes (hot flushes and night sweats) in a self-administered diary prior to commencing the trial and at T_4, T_8 and T_{12} weeks of the treatment period.

Secondary outcome measures and assessment of safety. Secondary outcome measures included serum estradiol levels, full blood count, fasting blood glucose (FBG), serum electrolytes, liver function tests and serum total cholesterol, HDL-cholesterol and LDL-cholesterol. Blood parameters were measured at T_0 and T_{12} weeks. Blood samples for pathology parameters were taken at the same time of day (between 8 am and 9 am) in a fasting state, to minimize the effect of the daily rhythm of hormone production. The blood samples were collected and analyzed by Queensland Medical Laboratories (QML) Pathology using standard validated protocols. Participants were asked to record any adverse events experienced over the 12-week study duration in diaries provided. Participants were also asked to complete a dietary survey for consumption of soy-based foods at baseline. Participants marked how often and the usual serving size for each of the following foods consumed within the previous 12 months: tofu, miso, green soybeans, fried tofu (tofu gan), soybean sprouts, foojook (tofu skin), western vegetarian meats, soybean drink or milk, fermented soybeans, roasted soybeans, black soybeans, okara and kinako (roasted soybean flour).

Sample size and statistical analysis. A minimum number of 49 participants per group were required to achieve a statistical power of 80% on the basis of a 20% improvement in symptoms as measured by the total domain score of the MENQOL. A modified intent-to-treat analysis was used where all participants who completed follow-up were analyzed as part of the group to which they were randomized. Demographic and clinical data were summarized by mean and standard deviation (SD), median and interquartile range (IQR) or as proportions. The MENQOL total and domain scores were analyzed using a generalized estimating equations (GEE) model with an autoregressive covariance structure to account for the multiple observations per person. Total flushes, day flushes and night sweats were analyzed using a GEE model with an auto-regression covariance structure and accounting for a Poisson distribution. The hormone data were nonparametric and analyzed using the Wilcoxon test. Correlations were assessed using Pearson's Coefficient. All analyses were conducted in R version 3.3.1.

RESULTS

Demographics

Of 180 women assessed for eligibility, a total of 115 women were eligible and inducted into the study (59 women in the active treatment group and 56 women in the placebo group). All women were experiencing menopausal symptoms including day hot flushes and/or night sweats and a combination of other menopausal symptoms at baseline (greater than mild on the MENQOL). Within the active treatment group, five women withdrew allowing follow-up for 54 evaluable participants and within the placebo group, six women withdrew allowing follow-up for 50 evaluable participants (see Fig. 1). The demographic characteristics between the active treatment and placebo groups were well matched at baseline (see Table 1). The mean age of women in the active treatment group was 53.2 ± 4.1 years, while for the placebo group it was 53.6 ± 4.0 years. Mean BMI was comparable at baseline between the active and placebo groups, 27.2 ± 5.6kg/m^2 versus 26.7 ± 4.2 kg/m^2, respectively. Women in both groups were predominantly non-smokers, classified themselves as social drinkers and reported undertaking regular weekly exercise. Baseline estradiol levels were below the limit of detection (LD) of 42 pmol/L for 46% of women in the active group and 41% of women in the placebo group.

Dietary assessment of isoflavone intake at baseline. Participants completed a dietary survey for consumption of soy-based isoflavones at the baseline visit. Women in both the active or placebo groups reported no consumption of the following soy-based foods as part of their normal diets: tofu, miso, green soybeans, fried tofu, soybean sprouts, foojook, western vegetarian meats, soybean drink or milk, fermented soybeans, roasted soybeans, black soybeans, okara or roasted soybean flour.

Efficacy of *Trigonella foenum-graecum* seed extract on menopausal symptoms. The presence and severity of menopausal symptoms were assessed at baseline, T_4, T_8 and T_{12} weeks using the validated MENQOL questionnaire. The results are summarized in Table 2. Total MENQOL scores were not statistically different between the active and placebo groups at baseline (17.8 ± 4.2 vs 17.5 ± 5.6, $p = 0.8$). A significant reduction in total MENQOL score was observed in the active treatment group (12.4 ± 4.0) compared with placebo (17.1 ± 5.5) over 12 weeks ($p < 0.001$). A multivariable model, adjusting for age, BMI category and estradiol level at baseline (± 42 pmol/L) produced the same result ($p < 0.001$). This was reflected in a significant reduction in symptoms across all four domains.

The Vasomotor domain consisted of the three questions regarding women being bothered by 'day flushes', 'night sweats' and 'sweating'. All three individual questions were significantly reduced in the active treatment group compared with the placebo group by T_{12} weeks of the treatment ($p < 0.001$). Within the Psychosocial domain, the four questions asking about emotional wellbeing; 'dissatisfaction with personal life' ($p = 0.041$), 'accomplishing less tasks' ($p = 0.029$),

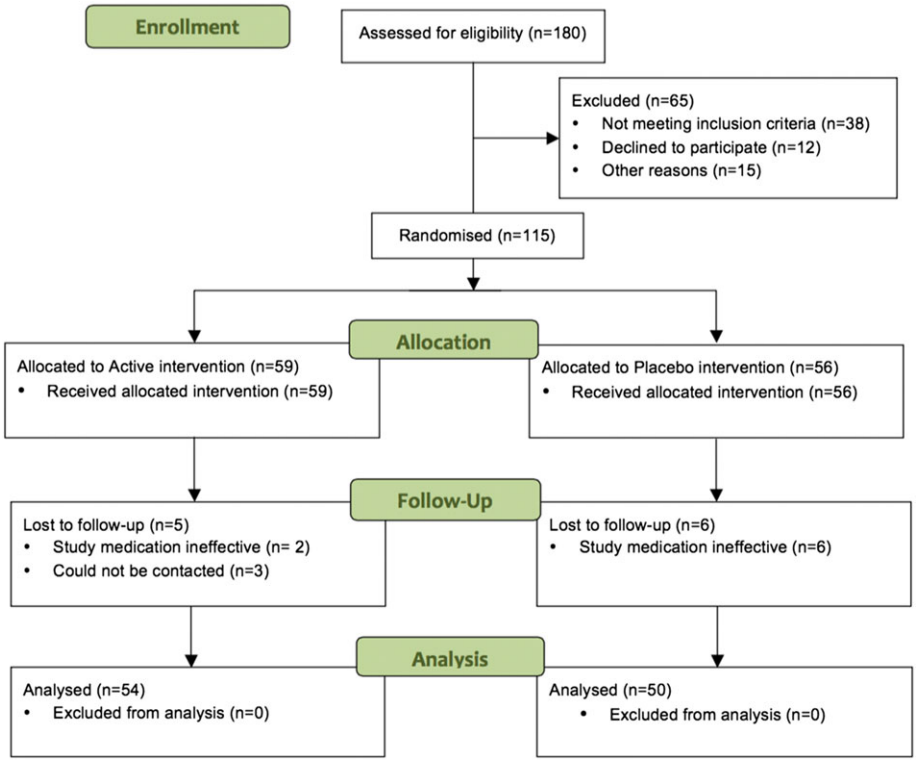

Figure 1. Flow diagram of participant recruitment, allocation, follow-up and analysis. [Colour figure can be viewed at wileyonlinelibrary.com]

Table 1. Baseline demographic characteristics of study participants in the *Trigonella foenum-graecum* de-husked seed extract supplemented group and placebo group

Characteristics	Active group (n = 54)	Placebo group (n = 50)
Age (years), mean ± SD	53.1 ± 4.1	53.6 ± 4.0
BMI (kg/m^2), mean ± SD	27.2 ± 5.6	26.7 ± 4.6
Weight (kg), mean + SD	72.9 ± 14.8	71.5 ± 13.7
Employed, *n* (%)	51 (94%)	48 (96%)
Relationship/partner, *n* (%)	46 (85%)	33 (66%)
Smoker, *n* (%)	5 (9%)	5 (10%)
Social drinker, *n* (%)	31 (57%)	29 (58%)
Regular exercise, *n* (%)	37 (69%)	33 (66%)

Table 2. Efficacy of *Trigonella foenum-graecum* de-husked seed extract supplementation compared with placebo in MENQOL total and sub-domain scores at T_0, T_4, T_8 and T_{12} weeks

Time		T_0 Mean ± SD	T_4 weeks Mean ± SD	T_8 weeks Mean ± SD	T_{12} weeks Mean ± SD	*P* value*
Vasomotor	Active	5.4 ± 1.5	4.1 ± 1.5	3.7 ± 1.4	3.3 ± 1.7	<0.001
	Placebo	4.8 ± 1.8	5.1 ± 1.7	5.0 ± 1.8	5.0 ± 1.8	
Psychosocial	Active	3.9 ± 1.8	3.2 ± 1.6	2.8 ± 1.4	2.9 ± 1.4	<0.001
	Placebo	4.2 ± 1.9	4.3 ± 2.1	4.1 ± 1.9	4.1 ± 1.9	
Physical	Active	4.1 ± 1.4	3.4 ± 1.2	3.1 ± 1.2	3.1 ± 1.2	<0.001
	Placebo	4.2 ± 1.6	4.0 ± 1.5	3.8 ± 1.5	3.9 ± 1.5	
Sexual	Active	4.4 ± 2.1	3.6 ± 1.8	3.0 ± 1.5	3.0 ± 1.7	<0.001
	Placebo	4.3 ± 2.4	4.4 ± 2.4	4.0 ± 2.4	4.1 ± 2.4	
Total	Active	17.8 ± 4.2	14.3 ± 4.0	12.6 ± 3.8	12.4 ± 4.0	<0.001
	Placebo	17.5 ± 5.6	17.8 ± 5.8	16.9 ± 5.8	17.1 ± 5.5	

Active treatment is 600 mg/day *Trigonella foenum-graecum* de-husked seed extract.
*Significance at $p < 0.05$, GEE, autoregressive covariance used.

'being impatient with other people' (p = 0.02) and 'feelings of wanting to be alone' (p = 0.021) were significantly improved in the active treatment group compared with the placebo group at T_{12} weeks. There was some improvement reported in regard to memory and questions relating to anxiety and depression in the active treatment group, but these were not statistically significant. Within the Physical domain, the 16 questions

related to energy; 'aching joints' (p = 0.006), 'feeling worn out' (p = 0.009), 'physical strength' (p = 0.010), 'stamina' (p < 0.001) and 'energy' (p = 0.003) were significantly improved in the active treatment group compared with the placebo group at T_{12} weeks. There were no significant changes reported in gastrointestinal discomfort, (flatulence and bloating), weight gain, musculoskeletal symptoms (aching joints, back pain) or the bladder symptoms. When the three questions are grouped together, the Sexual domain reports significant improvement in the active treatment group compared with placebo group at T_{12} weeks (p < 0.001).

Efficacy of *Trigonella foenum-graecum* seed extract on vasomotor symptoms. The participants completed a 7-day diary of vasomotor symptoms (hot flushes and night sweats) at four time points over the treatment period. The mean number of daily combined hot flushes and night sweats (total) were similar between both groups at baseline. Not all participants reported both day flushes and night sweats. Over the study period, a gradual significant reduction of approximately 50% in total flushes was observed in the active treatment group (p < 0.001). This was the result of a reduction in both the day flushes (p < 0.001) and night sweats (p < 0.001) (Fig. 2). These results are consistent with the results observed for the vasomotor domain of the MENQOL.

Secondary outcome measures

Efficacy of *Trigonella foenum-graecum* seed extract on estradiol levels. Baseline median levels of estradiol were 44 pmol/L (IQR = undetected-140 pmol/L) in the active group and 60 pmol/L (IQR = undetected-120 pmol/L) in the placebo group, with no statistically significant difference between groups (p = 0.5). At 12 weeks, median estradiol levels were 50 pmol/L (IQR = undetected-110 pmol/L) in the active group and 60 pmol/L (IQR = undetected-180 pmol/L) in the placebo group, showing no significant changes from baseline in either group (p = 0.5 and p = 0.4, respectively). There was a negative correlation between age and estradiol levels in both active and placebo groups (r^2 = −0.52, p < 0.001 and r^2 = −0.41, p < 0.003, respectively). This correlation was maintained at T_{12} weeks in the active and placebo groups (r^2 = −0.47, $p \leq 0.001$ and r^2 = −0.44, p = 0.002, respectively). There was no evidence of a correlation between estradiol levels and BMI for either group at any time point (p > 0.5).

Efficacy of *Trigonella foenum-graecum* seed extract on other health markers. This proprietary *T. foenum-graecum* seed extract was well tolerated over the 12-week study duration with no intervention-related adverse events recorded by participants. Pathology assessments for electrolyte/liver function and full blood count were within normal reference ranges in both groups at T_0 and remained within normal reference range at T_{12} weeks. Blood pressure remained stable throughout the duration of the trial for both the active treatment group (T_0 = systolic 123.0 ± 13.6 mmHg and diastolic 78.7 ± 8.1 mmHg; T_{12} = systolic 123.0 ± 10.8 and diastolic 79.9 ± 6.7 mmHg) and the placebo group (T_0 = systolic 121.6 ± 13.1 mmHg and diastolic 78.1 ± 7.7 mmHg; T_{12} = systolic 120.2 ± 10.2 and diastolic 77.8 ± 6.9 mmHg). Weight remained stable in both the placebo group (T_0 = 71.5 ± 13.7 kg; T_{12} = 71.5 ± 13.7 kg, p = 0.62) and the active treatment group (T_0 = 72.9 ± 14.8 kg; T_{12} = 74.1 ± 15.0 kg; p = 0.36). Fasting blood glucose, serum cholesterol, triglycerides, LDL-C and HDL-C remained stable and within normal ranges for both groups between baseline and T_{12} weeks.

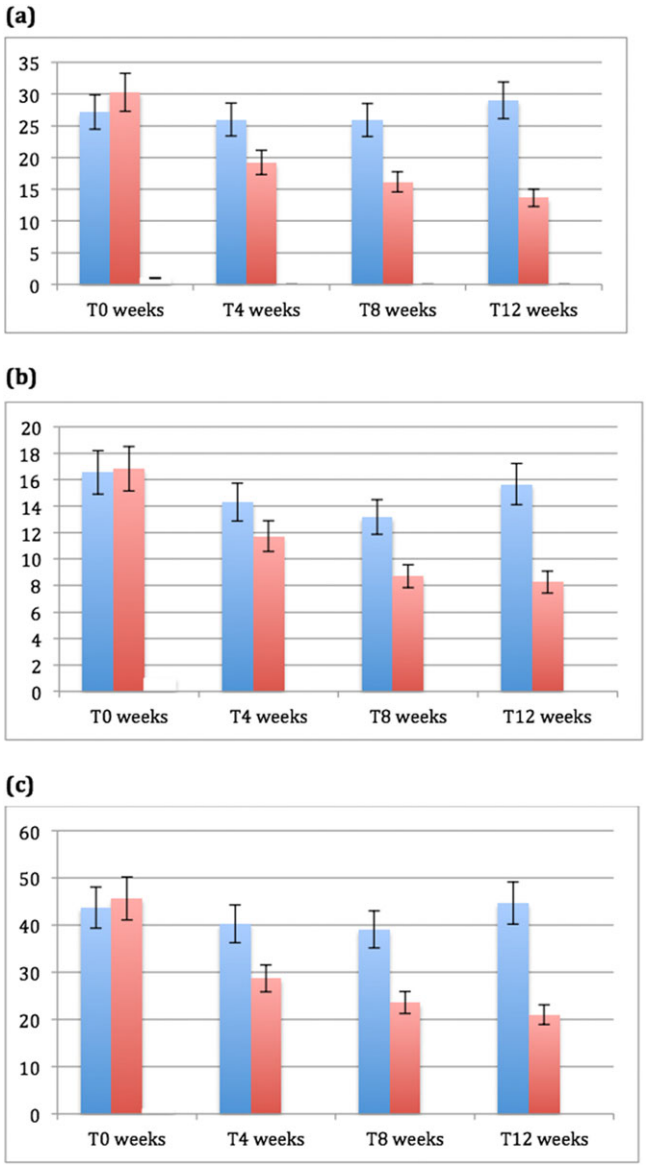

Figure 2. Efficacy of *Trigonella foenum-graecum* de-husked seed extract supplemented group and placebo group on patient-reported (over 7 days) number of vasomotor episodes at T_0, T_4, T_8 and T_{12} weeks. Legend: Active treatment is 600 mg/day of *Trigonella foenum-graecum* de-husked seed extract. A) Day-time flushes; B) Night sweats; C) Total day-time flushes and night sweats (over 7 days). Active group (orange), placebo group (blue). Significance at p < 0.05, GEE, auto-regression covariance, Poisson distribution used, 5% error bars. [Colour figure can be viewed at wileyonlinelibrary.com]

DISCUSSION

This is the first double-blind randomized, placebo controlled trial undertaken to demonstrate the therapeutic efficacy of this proprietary standardized *T.*

foenum-graecum de-husked seed extract in relieving menopausal symptoms in otherwise healthy women. These results support the growing body of evidence of a therapeutic role of *T. foenum-graecum* in hormonal processes including lactation (Turkylmaz *et al.*, 2011), female libido (Rao *et al.*, 2015), polycystic ovary syndrome (Swaroop *et al.*, 2015) and blood glucose regulation (Gaddam *et al.*, 2015).

In this study, *T. foenum-graecum* seed extract significantly reduced severity of vasomotor symptoms, a result that is supported by previous studies. (Hakimi *et al.*, 2006; Alizadeh and Mehraban, 2012). The study also found that majority of women reported difficulties in sexual functioning, supporting previous research that the transitional changes in hormone levels during menopause are associated with a negative effect on sexual function, including lubrication and desire for intimacy (Tepper *et al.*, 2012). Treatment with the *T. foenum-graecum* seed extract significantly improved sexual function in this study. Our previous research of the same *T. foenum-graecum* seed extract reported a significant increased libido in healthy menstruating women, which was associated with an increase in serum estradiol levels (Rao *et al.*, 2015). Interestingly, the estradiol data do not elaborate as to the mechanism of action of this *T. foenum-graecum* de-husked seed extract in reducing menopausal symptoms. The menopausal transition period is characterized by erratic estradiol production, lower progesterone metabolite excretion and an eventual rise in gonadotrophins, which is influenced by BMI (which results in lower hormone output) (Santoro *et al.*, 2017). Therefore, assessing the hormonal data in short-term studies is unlikely to provide meaningful data to assess the effect of *T. foenum-graecum* seed extract on estradiol levels in women experiencing menopausal symptoms.

There is emerging evidence of the importance of estrogen as both an antiinflammatory and neuroprotective agent (Hsieh *et al.*, 2017). Interestingly, a recent study showed that *T. foenum-graecum* seed extract significantly decreased serum pro-inflammatory cytokines (IL-1, IL-6 and TNF-α) and improved metabolic symptoms (including significantly blunting elevated blood glucose levels) in a similar manner to estrogen administration, in ovariectomized rats, a standard experimental model of menopause in rodents (Abedinzade *et al.*, 2015). Previous studies have reported that compromised glycemic control is also a mediator of hot flush severity during menopause and that diabetic women with elevated HbA1c demonstrated higher menopausal symptom severity scores (Rouen *et al.*, 2015). Recent studies have shown that *T. foenum-graecum* seed is effective in reducing the symptoms of diabetes mellitus (Verma *et al.*, 2016).

Longer duration studies in human populations are required to establish long-term reproductive and hormonal safety of *T. foenum-graecum*. A recent safety evaluation during the embryo-fetal development organogenesis period in pregnant Wistar rats has reported prenatal oral exposure during the organogenesis period was devoid of any maternal or fetal developmental side-effects (fetotoxicity or teratogenicity) (Deshpande *et al.*, 2016). Further, a recent preclinical safety assessment demonstrated No Observable Effect Level (NOEL) of 1 g/mg/day in acute oral toxicity studies and sub-chronic (90 days) in rats as well as reporting no mutagenicity (at 5 mg/plate in Ames test) and no structural chromosome aberrations (up to 2 g/culture) in human lymphocyte cells *in vitro* (Deshpande *et al.*, 2017). A review on the toxicological properties of *T. foenum-graecum*, reviewing both human and animal studies, suggests that the oral administration limit of *T. foenum-graecum* should be 21 g/per adult human weighing 60 kg to prevent any accidental overdose and subsequent side-effects. The dose in this study was 600 mg/per 70 kg (mean) that falls well below the suggested limit (Ouzir *et al.*, 2016).

A limitation of the study was the lack of definitive qualification of peri-menopausal and menopausal status. The small sample size, wide and fluctuating ranges in estradiol levels together with various blends of symptom profiles in this cohort did not allow for any sub-analysis of the data. It was expected to see a greater placebo effect, particularly in reduction in hot flushes (MacLennan *et al.*, 2004). To further understand the therapeutic activity of *T. foenum-graecum* seed extract on hormone levels, inflammatory markers and blood glucose levels, extended studies that span a significant duration of the menopause transition period may be required.

In summary, this study suggests that this proprietary *T. foenum-graecum* de-husked seed extract is an effective treatment for reducing vasomotor symptoms and associated menopausal symptoms in otherwise healthy women.

Conflicts of Interest

The authors declare no conflict of interest. The sponsor, Gencor Pacific, Hong Kong, supplied the investigational products and funded the study.

REFERENCES

Abedinzade M, Nasri S, Omodi MJ, Ghasemi E, Ghorbani A. 2015. Efficacy of *Trigonella foenum-graecum* seed extract in reducing metabolic and inflammatory alterations associated with menopause. *Iran Red Crescent Med J* **17**: e26685.

Alizadeh L, Mehraban Z. 2012. Effect of fenugreek (*Trigonella foenum-graecum*) on menopausal hot flash. Presentation. 9th European Congress on Menopause and Andropause. Athens, Greece.

Aradhana A, Rao AR, Kale RK. 1992. Diosgenin—a growth stimulator of mammary gland of ovariectomized mouse. *Indian J Exp Biol* **30**: 367–370.

Begum SS, Jayalakshmi HK, Vidyavathi HG, *et al.* 2016. A novel extract of fenugreek husk (FenuSMART^{TM}) alleviates postmenopausal symptoms and helps to establish the hormonal balance: a randomized, double-blind, placebo controlled study. *Phytother Res* **30**: 1775–1784.

Dean M, Murphy BT, Burdette JE. 2017. Phytosteroids beyond estrogens: regulators of reproductive and endocrine function in natural products. *Mol Cell Endocrinol* **442**: 98–105.

Deshpande P, Mohan V, Pore M, Gumaste S, Thakurdesai P. 2016. Prenatal developmental toxicity evaluation of furostanol saponin glycoside based standardized Fenugreek seed extract during organogenesis period of pregnancy in rats. *Int J Pharm Pharm Sci* **8**: 124–129.

Deshpande P, Mohan V, Ingavale D, Mane J, Pore M, Thakurdesai P. 2017. Preclinical safety assessment of furostanol glycoside-based standardised fenugreek seed extract in laboratory rats. *J Diet Suppl* **14**: 521–541.

Franco OH, Chowdhury R, Troup J, *et al.* 2016. Use of plant-based therapies and menopausal symptoms: a systematic review and meta-analysis. *JAMA* **315**: 2554–2563.

Gaddam A, Galla C, Thummisetti S, Marikanty RK, Palanisamy UD, Rao PV. 2015. Role of Fenugreek in the prevention of type 2 diabetes mellitus in prediabetes. *J Diabetes Metab Disord* **14**: 74–79.

Hakimi S, Alizadeh M, Delazar A, *et al.* 2006. Probable effects of fenugreek seed on hot flash in menopausal women. *JMP* **3**: 9–14.

Hilditch JR, Lewis J, Peter A, *et al.* 1996. A menopause-specific quality of life questionnaire: development and psychometric properties. *Maturitas* **24**: 161–175.

Hsieh YC, Hsieh FI, Chen YR, *et al.* 2017. Associations of estradiol levels and genetic polymorphisms of inflammatory genes with the risk of ischemic stroke. *J Biomed Sci* **24**:25.

Khosla P, Gupta DD, Nagpal RK. 1995. Effect of *Trigonella foenum-graecum* (fenugreek) on blood glucose in normal and diabetic rats. *Indian J Physiol Pharmacol* **39**: 173–174.

MacLennan AH, Broadbent JL, Lester S, Moore V. 2004. Oral oestrogen and combined oestrogen/progestogen therapy versus placebo for hot flushes. (Review) *Cochrane Database of Systematic Reviews* Issue 4. Art. No.: CD002978.

Ouzir M, El Bairi K, Amzazi S. 2016. Toxicological properties of fenugreek (*Trigonella foenum graecum*). *Food Chem Toxicol* **96**: 145–154.

Pandian RS, Anuradha CV, Viswanathan P. 2002. Gastroprotective effect of fenugreek seeds (*Trigonella foenum-graecum*) on experimental gastric ulcer in rats. *J Ethnopharmacol* **81**: 393–397.

Rao A, Steels E, Beccaria G, Inder W, Vitetta L. 2015. Influence of a specialized *Trigonella foenum-graecum* seed extract (Libifem), on testosterone, estradiol and sexual function in healthy menstruating women, a randomized placebo controlled study. *Phytother Res* **29**: 1123–1130.

Rietjens IM, Louise J, Beekmann K. 2016. The potential health effects of dietary phytoestrogens. *Br J Pharmacol* **174**:1263-1280.

Roberts H, Hickey M. 2016. Managing the menopause: an update. *Maturitas* **86**: 53–58.

Rouen PA, Krein SL, Reame NE. 2015. Postmenopausal symptoms in female veterans with type 2 diabetes: glucose control and symptom severity. *J Womens Health* **24**: 496–505.

Santoro N, Crawford SL, El Khoudary SR, *et al.* 2017. Menstrual cycle hormone changes in women transversing the menopause: study of women's health across the nation. *J Clin Endocrinol Metab* https://doi.org/10.1210/jc.2016-4017. [Epub ahead of print].

Sarri G, Pedder H, Dias S, Guoi Y, Lumsden. 2017. Vasomotor symptoms due to natural menopause; systematic review and network meta-analysis (NMA) of treatment effects from the NICE Menopause Guideline. *BJOG* https://doi.org/10.1111/1471-0528.14619 (Epub ahead of print).

Sharma RD, Raghuram TC, Rao NS. 1990. Effect of fenugreek seeds on blood glucose and serum lipids in type I diabetes. *Eur J Clin Nutr* **44**: 301–306.

Sreeja S, Anju VS, Sreeja S. 2010. In vitro oestradiolic activities of fenugreek *Trigonella foenum graecum* seeds. *Indian J Med Res* **131**: 814–819.

Swaroop A, Jaipuriar AS, Gupta SK, *et al.* 2015. Efficacy of a novel fenugreek seed extract (*Trigonella foenum-graecum*, Furocyst™) in polycystic ovary syndrome (PCOS). *Int J Med Sci* **12**: 825–831.

Tepper PG, Randolph JF Jr, McConnell DS, *et al.* 2012. Trajectory clustering of estradiol and follicle-stimulating hormone during the menopausal transition among women in the Study of Women's Health across the Nation (SWAN). *J Clin Endocrinol Metab* **97**: 2872–2880.

Tiran D. 2003. The use of fenugreek for breastfeeding woman. *Complement Ther Nurs Midwifery* **9**: 155–156.

Turkylmaz C, Onal E, Hirfanoglu IM, *et al.* 2011. The effect of galactagogue herbal tea on breast milk production and short-term catch-up of birth weight in the first week of life. *J Altern Complement Med* **17**: 139–142.

Verma N, Kauser Usman K, Patel N, *et al.* 2016. A multicenter clinical study to determine the efficacy of a novel fenugreek seed (*Trigonella foenum-graecum*) extract (Fenfuro™) in patients with type 2 diabetes. *Food Nutr Res* **60**: 32382.

Yadav UC, Baquer NZ. 2014. Pharmacological effects of *Trigonella foenum-graecum L*. in health and disease. *Pharm Biol* **52**: 243–254.

