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Efficacy of *Tribulus terrestris* for the treatment of hypoactive sexual desire disorder in postmenopausal women: a randomized, double-blinded, placebo-controlled trial

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Abstract

Objective: The objective of this study was to evaluate the efficacy of *Tribulus terrestris* for the treatment of hypoactive sexual desire disorder in postmenopausal women and evaluate its effect on the serum levels of testosterone.

Methods: We performed a prospective randomized, double-blinded, placebo-controlled study, during 18 months. A total of 45 healthy sexually active postmenopausal women reporting diminished libido were selected to participate in the study and were randomly assigned to receive 750 mg/d of *T terrestris* or placebo for 120 days. Randomization was performed using sealed envelopes. All participants answered the Female Sexual Function Index and the Sexual Quotient—female version questionnaires and had their serum levels of prolactin, thyroid-stimulating hormone, total testosterone, and sex hormone-binding globulin measured.

Results: A total of 36 participants completed the study, because 3 from each group were excluded due to side effects and 3 dropped out due to personal reasons. FSFI questionnaire results demonstrated an improvement in all domains in both groups ($P < 0.05$) except for lubrication which was improved only in the study group. QS-F results showed a significant improvement in the domains of desire ($P < 0.01$), arousal/lubrication ($P = 0.02$), pain ($P = 0.02$), and anorgasmia ($P < 0.01$) in women who used *T terrestris*, whereas no improvement was observed in the placebo group ($P > 0.05$). Moreover, free and bioavailable testosterone levels showed a significant increase in the *T terrestris* group ($P < 0.05$).

Conclusions: *Tribulus terrestris* might be a safe alternative for the treatment of hypoactive sexual desire disorder in postmenopausal women, because it was effective in reducing symptoms with few side effects. Its probable mechanism of action involves an increase in the serum levels of free and bioavailable testosterone.

Key Words: Hypoactive sexual desire disorder – Testosterone – Postmenopause – *Tribulus terrestris*.

The hypoactive sexual desire disorder (HSDD) is a common complex and multifactorial medical condition defined as persistent or recurrent disability of sexual fantasies/thoughts, and/or desire for or receptivity to sexual intercourse that may lead to personal distress.[1,2] HSDD may have negative impact on women's quality of life,[3,4] because lack of sexual desire affects their physical and emotional satisfaction and overall happiness.[5]

Hypoactive sexual desire disorder is the most common sexual dysfunction condition, affecting approximately 16% of women, whereas orgasm-related disorders represent 4% and dyspareunia comprises only 3%.[6] The Women's International Study of Health and Sexuality (WISHeS) showed that HSDD affects the quality of life among American and European women, and demonstrated a positive association between aging and the increase in prevalence of the disease.[7] A literature review that included 18 studies revealed that the prevalence of reduction in sexual desire increases after age 30.[8] A study that evaluated the prevalence and possible risk factors associated with sexual dysfunction showed an association between aging, menopause, and the prevalence of sexual disorders.[9]

Changes in sexual function that lead to an increase in HSDD in aging women might be secondary to a decline in estradiol levels associated with a decrease in androgen levels, during perimenopause.[10,11] Therefore, therapeutic strategies include the use of estrogen therapy, because it may have an effect on sexual desire by indirectly reducing vasomotor symptoms and by improving sleep quality and general well-being.[12] Estrogen therapy also addresses vaginal dryness caused by atrophic changes, which may secondarily improve sexual desire.[13,14] Another alternative is the use of testosterone, which seems to be effective for postmenopausal women with HSDD.[15] Nevertheless, both therapy strategies still present the risk of side effects such as endometrial cancer, breast cancer, cardiovascular disease, hirsutism, and acne.[15,16]

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Tribulus terrestris—a plant of the family Zygophyllaceae—has been used since ancient times as an aphrodisiac because of its ability to influence levels or mimic function of sex hormones. Indeed, it has been proposed that protodioscin—a steroidal saponin from *T terrestris*—increases endogenous androgen production by raising luteinizing hormone (LH) release.[17] Another possibility is that some *T terrestris* active components might be enzymatically converted into weak androgens that could be transformed into a more potent androgen such as testosterone.[17-19] However, these effects have not yet been confirmed and there are still concerns regarding the efficacy of using *T terrestris* for the treatment of HSDD.[20]

Therefore, the aim of the present study was to evaluate the efficacy of *T terrestris* in treating postmenopausal women with HSDD and investigate whether it affects the serum levels of testosterone.

METHODS

Study design

We performed a prospective randomized, double-blinded, placebo-controlled study evaluating the effects of treating postmenopausal women reporting HSDD with *T terrestris*. All participants read and signed an informed consent form. The study was approved by the research ethics committee of the Universidade Federal de Minas Gerais (UFMG) under COEP-224992, and registered at clinicaltrials.com under NCT01975694.

Participants

A total of 45 healthy sexually active postmenopausal women reporting diminished libido were selected to participate in the study. The study was conducted at the Clinic of Sexology of the Department of Gynaecology and Obstetrics—UFMG, Brazil, from May 2013 to December 2014. All participants were between 1 and 10 years since their last menstrual period, had a follicle-stimulating hormone level above 30 IU/L, estradiol levels below 40 pg/mL, and a body mass index less than 28 kg/m^2. None had used hormones or any drugs that could interfere with sexual desire within the previous year, were smokers or had hypertension. None had collagenosis, unbalanced endocrine system, pulmonary disease, renal disease, hepatic disease, vascular disease, history of breast or endometrial cancer, previous oophorectomy, history of myocardial infarction, or previous thromboembolic disease. Women reporting interpersonal relationship problems or those whose partners had sexual problems were not included in the study.

Evaluation and treatment

All women underwent clinical and gynecological examinations, and had mammography and vaginal ultrasound examinations before enrollment. Serum levels of prolactin, thyroid-stimulating hormone, total testosterone, and sex hormone-binding globulin were measured. The participants were randomly allocated into two groups, and the randomization was performed using sealed envelopes, so that neither the participant nor the examiner knew who was in the study or placebo group.

All the selected participants answered the Female Sexual Function Index (FSFI)[2] and the Sexual Quotient Female Version (QS-F)[21] questionnaires. The participants of the treatment group received 750 mg/d (three pills of 250 mg/d) of *T terrestris* (Androsten, Herbarium, Brazil) for 120 days (n = 25), whereas the participants in the control group received placebo during the same period of time (n = 20). Placebo and *T terrestris* were identical in appearance.

FSFI and QS-F questionnaires

The FSFI questionnaire was used to assess female sexual function. It is a well-established tool that has been validated for the Portuguese language[22] composed of 19 questions covering six domains of female sexual function: ''desire'', ''arousal'', ''lubrication'', ''orgasm'', ''satisfaction'' and ''pain''. The summary score ranges from 2 to 36, with low scores indicating severe female sexual dysfunction.

The QS-F is a 10-item questionnaire originally developed to assess sexual dysfunction of Brazilian women according to five domains: ''sexual desire'', ''arousal/lubrication'', ''pain'', ''orgasm'', and ''satisfaction''. The summary score ranges from 0 to 100, with low scores indicating more severe female sexual dysfunction.

Statistical analyses

We performed a Mann-Whitney *U* test to evaluate the independent variables, and the Wilcoxon test to evaluate

TABLE 1. *Female Sexual Function Index questionnaire results of postmenopausal women before and after treatment with* Tribulus terrestris *and placebo*

	Pretreatment			Post treatment		
Domains	*T terrestris* (n = 20)	Placebo (n = 16)	*P*	*T terrestris* (n = 20)	Placebo (n = 16)	*P*
Desire	2.04	1.95	0.77	3.66	3.15	0.25
Arousal	1.98	2.33	0.23	3.74	3.04	0.11
Lubrication	2.76	3.45	0.22	4.62	4.39	0.82
Orgasm	2.16	2.6	0.34	4.12	3.83	0.86
Satisfaction	2.88	3.2	0.44	4.66	4.03	0.19
Pain	3.80	3.45	0.53	5	4.5	0.50
Overall	15.62	16.98	0.37	25.8	22.93	0.44

P values were calculated using the Mann-Whitney *U* test.

TABLE 2. *Female Sexual Function Index questionnaire results of postmenopausal women before and after treatment with* Tribulus terrestris *and placebo*

	T terrestris (n = 20)			Placebo (n = 16)		
Domains	Pretreatment	Post treatment	*P*	Pretreatment	Post treatment	*P*
Desire	2.04	3.66	<0.01	1.95	3.15	<0.01
Arousal	1.98	3.74	<0.01	2.33	3.04	0.04
Lubrication	2.76	4.62	<0.01	3.45	4.39	0.05
Orgasm	2.16	4.12	<0.01	2.60	3.83	0.01
Satisfaction	2.88	4.66	<0.01	3.20	4.03	0.04
Pain	3.8	5.00	<0.01	3.45	4.5	0.02
Overall	15.62	25.8	<0.01	16.98	22.93	<0.01

P values were calculated using the Wilcoxon test.

the results from each participant before and after treatment in both groups (dependent variable). The analysis of variance (ANOVA) test was used to compare the results of the QS-F. Normal distribution and equality of variances were confirmed by the Kolmogorov-Smirnov and Levene tests, respectively. To compare categorical variables, we used the McNemar test. The results were considered significant if *P* is less than 0.05.

RESULTS

A total of 36 postmenopausal women (20 in the study group and 16 in the placebo group) with diagnosis of HSDD and age ranging from 43 to 65 years were included in this study. Nine patients were excluded: three dropped out due to personal reasons and six (three from each group) were withdrawn due to side effects (nausea). The mean age of the participants in both the study and the control groups was 54 ± 11 years. The total mean score and the scores of each of the six FSFI questionnaire domains obtained before and after treatment did not show any significant difference between the two groups ($P > 0.2$ and $P > 0.1$, respectively) (Table 1). We compared the effect of *T terrestris* and the placebo using the FSFI questionnaire, before and after treatment. Women receiving *T terrestris* scored significant improvements in all six domains. In the group of women who had used placebo, improvement was observed in all domains but ''lubrication'' (Table 2).

We also compared the effects of *T terrestris* and placebo using the QS-F questionnaire. Before treatment, the overall sexual quotient was 1.83 ± 0.76 in the group of women who were treated with *T terrestris*, and 1.79 ± 0.89 in the group that received placebo ($P = 0.53$). After 120 days of treatment with *T terrestris*, the QS-F indicated significant improvement in the domains ''desire'', ''arousal/lubrication'', ''pain'', and ''anorgasmia''. Women treated with placebo did not score improvements in any of the domains (Table 3).

TABLE 3. *Sexual Quotient Female Version questionnaire results of postmenopausal women before and after treatment with* Tribulus terrestris *and placebo*

		T terrestris (n = 20) Post treatment			Placebo (n = 16) Post treatment		
Domains	Pretreatment	(+)	(−)	Total	(+)	(−)	Total
Desire	(+)	5	9	14 (70%)	7	3	10 (62.5%)
	(−)	0	6	6 (30%)	1	5	6 (37.5%)
	Total	5 (25%)	15 (75%)	20 (100%)	8 (50%)	8 (50%)	16 (100%)
	P		<0.01			0.63	
Arousal/lubrication	(+)	4	7	11 (55%)	4	6	10 (62.5%)
	(−)	0	9	9 (45%)	1	5	6 (37.5%)
	Total	(20%)	(80%)	20 (100%)	5 (31.2%)	11 (68.8%)	16 (100%)
	P		0.02			0.13	
Pain	(+)	2	9	11 (55%)	4	5	9 (56.3%)
	(−)	1	8	9 (45%)	0	7	7 (43.7%)
	Total	3 (15%)	17 (85%)	20 (100%)	4 (25%)	12 (75%)	16 (100%)
	P		0.02			0.06	
Orgasm	(+)	10	8	18 (90%)	6	7	13 (81.3%)
	(−)	0	2	2 (10%)	1	2	3 (18.7%)
	Total	10 (50%)	10 (50%)	20 (100%)	7 (43.7%)	9 (56.7%)	16 (100%)
	P		<0.01			0.07	
Satisfaction	(+)	8	8	16 (80%)	8	7	15 (93.8%)
	(−)	2	2	(20%)	1	0	1 (6.2%)
	Total	10 (50%)	10 (50%)	20 (100%)	9 (56.3%)	7 (43.7%)	16 (100%)
	P		0.11			0.07	

P values were calculated using the McNemar test.
(+), presence of sexual problem related to the domain; (−), absence of sexual problem related to the domain.

TABLE 4. *Serum levels of total, free and bioavailable testosterone levels obtained in postmenopausal women before and after treatment with* Tribulus terrestris *and placebo*

	T Terrestris (n = 20)			Placebo (n = 16)		
Testosterone	Pretreatment	Post treatment	*P*	Pretreatment	Post treatment	*P*
Total	12 ± 5.7	14.2 ± 6.9	0.08	12.8 ± 6.9	11.7 ± 6.2	0.08
Free	0.2 ± 0.1	0.2 ± 0.2	0.04	0.2 ± 0.1	0.2 ± 0.2	0.28
Bioavaible	4.7 ± 3.3	5.4 ± 4.3	0.04	5.0 ± 3.4	4.7 ± 3.5	0.28

P values were calculated using the Wilcoxon test.

The total testosterone levels in both the *T terrestris* and the placebo groups did not vary before and after the treatment. However, we observed a significant increase in the levels of free and bioavailable testosterone in the group of women who received *T terrestris*, whereas no increase was detected in the placebo group (Table 4).

DISCUSSION

To our knowledge, this is the first study suggesting that *T terrestris* might be an effective treatment for postmenopausal women with HSDD. Moreover, our results indicate that the improvement observed may be secondary to an increase in the serum levels of free and bioavailable testosterone. The *T terrestris* treatment used herein seems to be safe, because only six women (three from each group) withdrew from the study due to mild side effects (nausea), which was unlikely to be due to the medicine.

We used the FSFI questionnaire as it was designed to address the multidimensional nature of female sexual function in clinical trials.[2] No difference was observed in the FSFI scores between the groups before treatment, thus confirming that both groups were homogeneous and that there was no selection bias that could interfere with the results. When we compared both groups after treatment, we also did not observe differences. This result demonstrates that both groups were still homogeneous after treatment probably due to a similar response to *T terrestris* and placebo. After treatment, women who received *T terrestris* for 120 days had improved scores in all the domains and in the total mean FSFI score. Women using placebo showed improvement in the total mean score and in all domains of FSFI, except ''lubrication''. These results demonstrate that enhancement of ''lubrication'' is directly related to the use of *T terrestris*. We believe that the use of placebo probably exerted an indirect reduction in the participants' personal distress, making them more permissive to stimulation and sexual motivation, thereby improving sexual function. However, any improvement in ''lubrication'' was likely due to physiological triggers, which were probably affected directly by the use of *T terrestris*.

Similar results for the total mean FSFI scores have been described by Gama et al[23] who studied 144 patients that used *T terrestris* for 90 days. The FSFI results after therapy revealed a significant improvement in the scores of 88% of the patients. The authors, however, evaluated only premenopausal women and did not perform a placebo control group. The individual results we obtained for each domain were similar to those described by Akhtari et al[24] who performed a randomized controlled trial with 60 women using *T terrestris* and placebo for 4 weeks. However, these authors only evaluated premenopausal women.

We also used the QS-F questionnaire, a tool designed to assess sexual function of Brazilian women.[6] Similar to the FSFI scores, no difference was observed in the QS-F scores between the groups before treatment, confirming that both groups were homogeneous. After treatment, women in the group who received *T terrestris* demonstrated an improvement in the QS-F scores for ''desire'', ''excitation/lubrication'', ''pain'', and ''anorgasmia'', whereas no improvement was observed in the group treated with placebo. This suggests *T terrestris* might have efficacy for improving sexual function. There are no previous studies using QS-F to analyze postmenopausal women with HSDD treated with *T terrestris*, and, because this questionnaire was formulated specifically for Brazilian women, we believe that this scale is more representative for our sample, and might explain the difference observed for both questionnaires.

Although the use of *T terrestris* did not interfere with the serum levels of total testosterone, we observed a significant increase in the serum levels of free and bioavailable testosterone. The effects of *T terrestris* in the testosterone levels in women have not been evaluated previously.[20] We suggest that an increase in the active form of the hormone underlies the improvement in sexual function observed in the women who used *T terrestris*.

CONCLUSIONS

In conclusion, our study is the first to suggest that *T terrestris* might be a safe alternative for the treatment of HSDD in postmenopausal women, because it was effective in reducing the symptoms, with few side effects, probably through a mechanism leading to an increase in the levels of free and bioavailable testosterone. As we studied a limited number of women, more studies with a higher number of women are necessary to confirm our results.

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