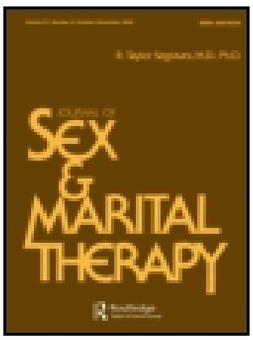

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Effect of Tribulus Terrestris in the Treatment of Female Sexual Dysfunction and Clitoral Vascularization. Results of a Randomized Study Comparing Two Different Dosage Regimes

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ABSTRACT

We evaluated the efficacy of *Tribulus terrestris* in two different dosage regimes for the treatment of sexual dysfunction in pre and postmenopausal women and its effect on the vascular resistance of the clitoral artery using Power Doppler. A total of 104 women were randomly assigned to receive 94mg, three times/day (TT3) or 280mg once/day for 90 days (TT1). Evaluation was performed using FSFI and QS-F questionnaires, serum levels of prolactin, TSH, total testosterone and SHBG, and clitoral artery assessment with Power Doppler ultrasound. FSFI results demonstrated an improvement in all domains in both groups ($P < 0.05$) except for the "Satisfaction" in the TT3 premenopausal group. QS-F results showed a significant improvement in the mean total score in women of both reproductive phases, for both groups. Postmenopausal patients improved in all sexual domains, except for "orgasm" in the TT1 group. PI of the clitoral artery showed no difference in both reproductive phases, in both groups. We conclude that TTerrestris can be a safe alternative for the treatment of sexual dysfunction in pre and postmenopausal women as it is effective in reducing the symptoms with no side effects. Moreover, its use, increased total, free and bioavailable testosterone.

Introduction

Female sexual dysfunction (FSD) refers to a change in the sexual response associated with personal suffering. Includes lack of sexual desire, difficulty or lack of arousal/lubrication, difficulty or inability to reach orgasm and/or pain during sexual activity (American Psychiatric Association, 2013). It is caused by an imbalance of a complex interaction of anatomical, endocrine, neuronal, vascular, psychological and social factors (Clayton & Groth, 2013). Sexual complaints are reported by approximately 40% of women worldwide, and approximately one in eight women at some point in life experience some sexual dysfunction (Fugl-Meyer et al., 2004; Laumann et al., 2005; Nappi et al., 2016; Shifren, Monz, Russo, Segreti, & Johannes, 2008; Wolpe, Zomkowski, Silva, Queiroz, & Sperandio, 2017; Zhang et al., 2017).

FSD is classified as sexual desire dysfunction, arousal dysfunction, orgasm dysfunction and sexual pain dysfunction (American Psychiatric Association, 2013). This classification is based

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on a better understanding of the sexual response and the recognition of the cyclical model proposed by Basson, Wierman, van Lankveld, and Brotto (2010). Recently the American Psychiatric Association (APA) guidelines require that, in order to be considered a sexual dysfunction, the sexual complaint must be recurrent or persistent, cause personal suffering or interpersonal difficulty and the problem must be present for at least six months1. A careful approach and the use of available therapies can improve the sexual function of many women. The use of herbal medicines, especially *Tribulus terrestris* (TTerrestris), has been proposed to improve sexual response and may be an alternative for the treatment of FSD (Akhtari et al., 2014; De Sousa & Lima, 2017; De Souza, Vale, & Geber, 2016; Gama et al., 2014; Mazaro-Costa, Andersen, Hachul, & Tufik, 2010; Postigo et al., 2016; Vale, Zanolla Dias de Souza, Rezende, & Geber, 2018).

Tribulus terrestris is a medicinal herb in the family Zygophyllaceae. Protodioscin is the dominant component of the herb, considered the main pharmacologically active steroid saponin (Dinchev et al., 2008). Some studies suggested that protodioscin regulates the hormonal balance without interfering with the physiological mechanisms of hormonal regulation and stimulates the enzyme 5-a-reductase, which converts testosterone into dehydrotestosterone, increasing endogenous levels of biologically active testosterone (Antonio, Uelmen, Rodriguez, & Earnest, 2000; Qureshi, Naughton, & Petroczi, 2014; Semerdjieva & Zheljazkov, 2019). Testosterone is the primary hormone that modulates the sex drive response in the brain, triggering sexual desire. It is also essential in modulating the physiology of the clitoris and vagina to facilitate engorgement, genital arousal and lubrication (Nappi et al., 2003). Previous animal and human studies also suggested that protodioscin stimulates the release of nitric oxide into the endothelium of genital vessels, increasing vascularity and promoting genital engorgement (Adaikan, Gauthaman, Prasad, & Ng, 2000; Sahin et al., 2016; Semerdjieva & Zheljazkov, 2019). The use of Doppler technique allowed the study of clitoral artery to assess its vasculature and clitoral function, however this method has not been used to evaluate the effects of *Tribulus terrestris* (Khalifé, Binik, Cohen, & Amsel, 2000; Souto, Palma, & Riccetto, 2010).

There are several herbal supplements and pharmaceutical preparations available using the TTerrestris that have been used to try to improve libido in women. However, data in the literature are still scarce with regard to its effectiveness for the treatment of female sexual dysfunction (Ștefănescu, Tero-Vescan, Negroiu, Aurică, & Vari, 2020). Most studies generally use teas or plant extracts that have a possible action on female sexual response, with few studies using the formulation in accordance with the worldwide standardization criteria for the treatment of female sexual dysfunction (De Souza et al., 2016; Neychev & Mitev, 2016; Postigo et al., 2016; Vale et al., 2018; Zhu, Du, Meng, Dong, & Li, 2017).

Based on this knowledge of the protodiocin mechanism of action on the sexual response, we performed this study to evaluate the effect of *Tribulus terrestris*, in two different dosage regimes, on the treatment of women with FSD using the FSFI and Q-SF questionnaire, hormonal evaluation and on the vascular analysis of the clitoral artery using ultrasound with power Doppler.

Material and methods

Study design

We performed a prospective, randomized, open study to evaluate the effects of treating women reporting FSD with *Tribulus terrestris*. All participants signed an informed consent form and 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 NCT2625016. The study was conducted at the Clinic of Sexology of the Department of Gynecology and Obstetrics - UFMG, Brazil, from January 2019 to September 2019.

Participants

A total of 104 sexually active, healthy women with FSD were selected to participate in the study. A total of 52 were premenopausal, with regular menstrual cycles, without using hormonal

contraceptive methods or regular use of any medication. The remaining 52 were postmenopausal, with more than 12 months of amenorrhea and 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, alcohol consumers, or had hypertension, collagenosis, unbalanced endocrine system, pulmonary disease, renal disease, hepatic disease, vascular disease, history of breast or endometrial cancer, previous bilateral oophorectomy, history of myocardial infarction, previous thromboembolic disease, depression or psychiatric disease. All women included had a stable marital relationship for at least two years and had a normal gynecological examination.

Assessment and treatment

Participants who met the inclusion criteria and who signed the consent form were invited to answer the FSFI and QS-F questionnaires. All participants underwent clinical and gynecological examinations, and had mammography, vaginal ultrasound examination to assess vascularization of the clitoral artery using the power doppler. Serum levels of prolactin, thyroid stimulating hormone, total testosterone, sex hormone-binding globulin (SHBG), free and bioavailable testosterone were measured. The 52 participants of both reproductive phases were randomly allocated in two groups using computer-generated *random* numbers. Thus, in the group of premenopausal women, 26 participants received *Tribulus terrestris* 94 mg, three times a day, for 90 days (Group TT3) and the other 26 received *Tribulus terrestris* 280 mg, once a day, for 90 days (Group TT1). Likewise, in the group of postmenopausal women, 26 participants received *Tribulus terrestris* 94 mg, three times a day, for 90 days (TT3) and another 26 received *Tribulus terrestris* 280 mg, once a day, for 90 days (TT1). Patients in both groups used the same dosage of the active drug (prodioscin 112 mg/day). After 90 days of using TT, the participants repeated the FSFI and QS-F questionnaires, the vaginal ultrasound examination to assess vascularization of the clitoral artery using the power doppler and the serum hormone levels.

FSFI and QS-F questionnaires

The FSFI questionnaire was used to assess female sexual function. It is a well-established tool that consists of 19 questions covering six domains of female sexual function: "desire", "arousal", "lubrication", "orgasm", "satisfaction" and "pain". Higher scores denote better degree of sexual function and lower scores indicate severe sexual dysfunction (Rosen, Brown, & Heiman, 2000). The QS-F is a 10-item questionnaire originally developed to assess the sexual dysfunction of Brazilian women according to five domains: "sexual desire", "arousal / lubrication", "pain", "orgasm", "satisfaction". The summary score ranges from 0 to 100, with low scores indicating more severe female sexual dysfunction (Abdo, 2006).

Doppler clitoral artery

All examinations were performed by the same examiner, at the same time of the day using the same ultrasound device (Medison Acuvix XG, Samsung) to avoid interobserver and interdevice variations and any possible changes caused by the participant's circadian cycle (Khalifé et al., 2000; Woodard & Diamond, 2009). The room where the examinations were performed was kept in half-light and constant temperature (around 20ºC).

The clitoral artery was studied using a 5 to 9 MHz multifrequency endocavitary convex transducer with color flow and Power Doppler mapping. All participants were placed in the lithotomy position. The transducer probe was placed sagittally to the clitoris (Doppler angle <60 degrees), without exerting pressure on the genital tissues, allowing the identification of the clitoral artery flow. Once the clitoral artery was located, at least three sequential waveforms were

obtained to measure the peak systolic velocity, final diastolic velocity and mean velocity of the artery, in order to calculate the pulsatility index (PI) and vascular flow velocity (VFV).

Statistical analysis

Sample size was calculated considering clinical improvement as the main dependent variable based on the results previously described (De Souza et al., 2016; Vale et al., 2018). Thus, for a test with effect size of 0.2, power test of 0.90 and alpha power of 0.05 (p values) the minimum requirement was 21 patients in each group. In order to guarantee the minimum sample of 84 patients, considering the possible drop-out rate, we included 104 patients.

Student t-test were performed for independent samples and Fisher's exact test to compare the difference between means of the two groups (TT3 and TT1). The normal distribution and the equality of variances were confirmed by the Kolmogorov-Smirnov and Levene tests. The Mann-Whitney test was used to evaluate the independent variables and the Wilcoxon test was used to analyze the results of each patient before and after treatment in both. groups (dependent variable). To compare association, relationship and dependence we used Pearson's chi-square test.

Results

A total of 104 women with FSD were included in the study. Nineteen patients were excluded: 10 did not return for the second evaluation and 9 did not use the medication correctly. Therefore, 85 women with FSD were analyzed, 42 were premenopausal and 43 postmenopausal. No patient reported side effects with the use of the medication in all groups. The mean age of premenopausal women was 38.9 ± 7.4 years and of the postmenopausal women was 56 ± 5.3. The mean BMI of the premenopausal women was 26 ± 4.2 and of the postmenopausal women was 26.6 ± 4.3.

When we compared the results obtained from the FSFI and QS-F questionnaires, before and after treatment, in women of both reproductive phases, we observed a significant improvement in the total mean score (Table 1). Moreover, the results obtained in the mean total score and for each of the six domains of the FSFI questionnaire, before and after treatment, in both reproductive phases, for both groups, showed significant improvements, except for the "Satisfaction" domain in the TT3 premenopausal group (Table 2).

The results obtained for the mean total score and for each of the six domains of the QS-F questionnaire, in women of both reproductive phases, for both groups, demonstrated significant improvements in the mean total score, after treatment. However, premenopausal patients of the TT3 group did not experienced improvement in the domains of "desire" and "orgasm", and of the TT1 group did not showed improvement in the "pain" domais. Postmenopausal patients improved in all sexual domains, except for "orgasm" in the TT1 group (Table 3).

Serum levels of Prolactin, TSH and SBGH did not vary significantly before and after treatment, in women of both reproductive phases, in both groups of patients (Table 4 and Table 5). We observed a significant increase in the levels of total, free and bioavailable Testosterone in women of both reproductive phases after treatment (Table 4). However, when we compared both groups, we observed a significant increase in the levels of total, free and bioavailable Testosterone only in the TT1 group for pre and postmenopausal women (Table 5).

Table 1. Female Sexual Function Index and Sexual Quotient Female Version questionnaire results of premenopausal and postmenopausal women before and after treatment with Tribulus terrestris

		Premenopausal (n = 42)		Postmenopausal (n = 43)	
Questionnaire	Day	Mean ± SD	p	Mean ± SD	p
FSFI	0	18.1 ± 5.9	<0.001	15.4 ± 7.6	<0.001
	90	24.8 ± 5.8		24.8 ± 7.2	
QS-F	0	51.9 ± 18.8	<0.001	52.4 ± 19.2	0.001
	90	66.6 ± 21.6		70.6 ± 21.7	

Wilcoxon test. SD = Standard Deviation

Table 2. Female Sexual Function Index questionnaire results of premenopausal and postmenopausal women before and after treatment with Tribulus terrestris one and three times/day.

			Premenopausal (n = 42)			Postmenopausal (n = 43)	
Variable		Day	n	Mean ± SD	p	n	Mean ± SD	p
	TT3	0	21	2.11 ± 0.8	0.002	21	2.23 ± 0.93	0.001
		90	21	3.29 ± 1.31		21	3.31 ± 1.18	
Desire	TT1	0	21	2.29 ± 0.82	0.003	22	2.29 ± 0.8	0.001
		90	21	3.23 ± 1.24		22	3.16 ± 1.02	
	TT3	0	21	2.71 ± 1.23	0.016	21	2.36 ± 1.4	0.001
		90	21	3.54 ± 1.21		21	3.71 ± 1.39	
Arousal	TT1	0	21	2.42 ± 0.98	0.001	22	2.25 ± 1.48	0.001
		90	21	3.66 ± 1.15		22	4.02 ± 1.32	
	TT3	0	21	3.11 ± 1.59	0.003	21	1.79 ± 1.12	0.001
		90	21	4.46 ± 1.7		21	4.1 ± 1.79	
Lubrication	TT1	0	21	3.01 ± 1.69	0.001	22	3.62 ± 1.99	0.001
		90	21	4.64 ± 1.19		22	4.21 ± 1.87	
	TT3	0	21	2.97 ± 1.61	0.011	21	2.84 ± 1.88	0.008
		90	21	3.92 ± 1.78		21	3.96 ± 1.68	
Orgasm	TT1	0	21	2.55 ± 1.18	0.002	22	2.6 ± 2.09	0.001
		90	21	3.77 ± 1.42		22	4.67 ± 1.51	
	TT3	0	21	3.49 ± 1.51	0.075	21	3.28 ± 1.34	0.01
		90	21	4.27 ± 1.01		21	4.3 ± 1.26	
Satisfaction	TT1	0	21	3.22 ± 1.1	0.003	22	2.76 ± 1.46	0.001
		90	21	4.4 ± 1.07		22	4.33 ± 1.51	
	TT3	0	21	4.13 ± 2.02	0.006	21	2.51 ± 1.76	0.001
		90	21	5.47 ± 1.07		21	4.95 ± 1.01	
Pain	TT1	0	21	4.1 ± 1.77	0.049	22	3.33 ± 2.19	0.001
		90	21	4.86 ± 1.49		22	4.76 ± 1.81	
	TT3	0	21	18.5 ± 6.8	0.002	21	15 ± 6.5	0.001
		90	21	24.9 ± 6.3		21	24.3 ± 6.4	
Overall	TT1	0	21	17.6 ± 5.1	0.001	22	15.9 ± 8.6	0.001
		90	21	24.6 ± 5.4		22	25.2 ± 7.9	

Wilcoxon test. SD = Standard Deviation

Table 3. Sexual Quotient Female Version questionnaire results of premenopausal and postmenopausal women before and after treatment with Tribulus terrestris one and three times/day.

			Premenopausal (n = 42)			Postmenopausal (n = 43)	
Variable		Day	n	Mean ± SD	p	n	Mean ± SD	p
	TT3	0	21	2.50 ± 1.1	0.124	21	2.62 ± 1.50	0.015
		90	21	3.05 ± 1.59		21	3.55 ± 1.59	
Desire	TT1	0	21	1.67 ± 1.09	0.036	22	2.25 ± 1.46	0.006
		90	21	2.45 ± 1.52		22	3.41 ± 1.34	
	TT3	0	21	3.21 ± 1.35	0.027	21	2.60 ± 0.98	0.008
		90	21	3.86 ± 1.42		21	3.11 ± 1.27	
Arousal	TT1	0	21	2.77 ± 0.94	0.003	22	3.51 ± 1.08	0.002
		90	21	3.71 ± 0.94		22	4.01 ± 1.37	
	TT3	0	21	2.10 ± 1.84	0.131	21	2.33 ± 1.65	0.133
		90	21	2.57 ± 1.75		21	2.81 ± 1.81	
Orgasm	TT1	0	21	1.76 ± 1.58	0.004	22	2.50 ± 1.82	0.001
		90	21	2.90 ± 1.70		22	3.86 ± 1.49	
	TT3	0	21	2.10 ± 1.87	0.049	21	3.28 ± 1.34	0.01
		90	21	2.90 ± 1.89		21	4.30 ± 1.26	
Satisfaction	TT1	0	21	1.86 ± 1.42	0.01	22	2.76 ± 1.46	0.001
		90	21	2.95 ± 1.80		22	4.33 ± 1.51	
	TT3	0	21	3.43 ± 2.09	0.014	21	2.43 ± 1.89	0.018
		90	21	4.29 ± 1.27		21	3.57 ± 1.66	
Pain	TT1	0	21	3.52 ± 1.81	0.605	22	2.41 ± 1.79	0.019
		90	21	3.71 ± 1.85		22	3.59 ± 1.74	
	TT3	0	21	56.7 ± 19.8	0.012	21	49.6 ± 19.4	0.004
		90	21	68.5 ± 23.2		21	66.2 ± 20.7	
Overall	TT1	0	21	47.0 ± 16.8	0.002	22	55.0 ± 19.1	0.001
		90	21	64.7 ± 20.2		22	74.8 ± 22.4	

Wilcoxon test. SD = Standard Deviation

Table 4. Hormone serum levels of premenopausal and postmenopausal women before and after treatment with Tribulus terrestris

		Premenopausal (n = 42)		Postmenopausal (n = 43)	
Hormones	Day	Mean ± SD	p	Mean ± SD	p
Prolactin	0	12.1 ± 6.6	0.342	8.3 ± 3.8	0.282
	90	11.2 ± 4.5		8.0 ± 3.7	
TSH	0	1.73 ± 0.84	0.233	1.94 ± 1.21	0.664
	90	1.64 ± 0.96		1.89 ± 1.01	
SHBG	0	62.0 ± 45.1	0.082	49.3 ± 17.9	0.17
	90	55.9 ± 35.6		48.1 ± 23.3	
Total T1	0	19.1 ± 8.8	0.003	18.3 ± 9.3	0.009
	90	21.8 ± 8.9		20.2 ± 9.5	
Free T1	0	0.26 ± 0.15	0.005	0.25 ± 0.15	0.003
	90	0.33 ± 0.18		0.31 ± 0.18	
Bioavailable T1	0	5.9 ± 3.9	0.007	6.2 ± 3.3	0.033
	90	7.6 ± 4.3		6.9 ± 3.4	

Wilcoxontest. SD = Standard Deviation. T1 = Testosterone.

Table 5. Hormone serum levels of premenopausal and postmenopausal women before and after treatment with Tribulus terrestris one and three times/day.

				Premenopausal (n = 42)			Postmenopausal (n = 43)	
Variable		Day	n	Mean ± SD	p	n	Mean ± SD	p
	TT3	0	21	11.8 ± 7.0	0.404	21	9.6 ± 4.2	0.37
		90	21	10.4 ± 3.0		21	9.4 ± 4.3	
Prolactin	TT1	0	21	12.3 ± 6.2	0.566	22	7.1 ± 3.0	0.653
		90	21	11.9 ± 5.5		22	6.6 ± 2.3	
	TT3	0	21	1.55 ± 0.60	0.59	21	2.07 ± 0.91	0.614
		90	21	1.48 ± 0.59		21	2.17 ± 1.02	
TSH	TT1	0	21	1.91 ± 1.00	0.279	22	1.82 ± 1.45	0.249
		90	21	1.80 ± 1.21		22	1.62 ± 0.96	
	TT3	0	21	58.3 ± 37.5	0.147	21	47.7 ± 21.1	0.171
		90	21	53.5 ± 38.2		21	44.0 ± 19.1	
SHBG	TT1	0	21	65.8 ± 52.3	0.391	22	50.9 ± 14.4	0.365
		90	21	58.4 ± 33.4		22	52.0 ± 26.5	
	TT3	0	21	20.4 ± 7.6	0.126	21	18.7 ± 8.9	0.186
		90	21	21.9 ± 5.8		21	20.5 ± 10.3	
TotalT1	TT1	0	21	17.8 ± 9.8	0.008	22	18.0 ± 9.9	0.017
		90	21	21.7 ± 11.3		22	19.9 ± 8.9	
	TT3	0	21	0.29 ± 0.16	0.112	21	0.26 ± 0.17	0.052
		90	21	0.35 ± 0.18		21	0.34 ± 0.20	
FreeT1	TT1	0	21	0.24 ± 0.14	0.013	22	0.25 ± 0.13	0.021
		90	21	0.31 ± 0.19		22	0.29 ± 0.15	
	TT3	0	21	6.6 ± 4.0	0.156	21	6.8 ± 3.6	0.511
		90	21	8.0 ± 4.2		21	6.9 ± 3.3	
BioavailableT1	TT1	0	21	5.3 ± 3.7	0.012	22	5.6 ± 2.9	0.023
		90	21	8.0 ± 4.2		22	6.9 ± 3.4	

Wilcoxontest. SD = StandardDeviation. T1 = Testosterone

The Pulsatility Index of the clitoral artery, in women of both reproductive phases, showed no difference when comparing the results obtained before and after treatment. Also, we observed a reduction in Vascular Flow Velocity, after treatment, in postmenopausal women (Table 6). However, when we compared the three indexes, in both groups of both reproductive phases, we did not observe any difference in the proportion of patients who showed a difference in the results before and after treatment (Table 7).

Discussion

To our knowledge, this is the first study that that evaluates the use of TTerrestris in the physiological parameters of female sexual response, including clitoral blood flow. Our results confirm

Table 6. Results of the clitoral artery Doppler in premenopausal and postmenopausal women before and after treatment with Tribulus terrestris

		Premenopausal (n = 42)		Postmenopausal (n = 43)	
Doppler Index	Day	Mean ± SD	p	Mean ± SD	p
PI	0	2.24 ± 1.18	0.228	2.22 ± 0.66	0.174
	90	2.02 ± 1.01		2.02 ± 0.87	
RI	0	0.79 ± 0.10	0.335	0.83 ± 0.09	0.086
	90	0.78 ± 0.13		0.79 ± 0.11	
VFV	0	9.14 ± 4.34	0.5	7.77 ± 2.97	0.016
	90	8.77 ± 3.79		6.35 ± 2.09	

Wilcoxon test. SD = Standard Deviation

Table 7. Results of the clitoral artery Doppler in premenopausal and postmenopausal women before and after treatment with Tribulus terrestris one and three times/day

		Premenopausal (n = 42)						Postmenopausal (n = 43)					
		TT3		TT1		Total		TT3		TT1		Total	
Variable		n	%	n	%	n	%	n	%	n	%	n	%
PI													
	before < after	8	38,1	6	28,6	14	33,3	7	33,3	8	36,4	15	34,9
	before>after	13	61,9	15	71,4	28	66,7	14	66,7	14	63,6	28	65,1
	Total	21	100	21	100	42	100	21	100	22	100	43	100
	p		0.51						0.83				
RI													
	before < after	8	38,1	8	38,1	16	38,1	6	28,6	9	40,9	15	34,9
	before>after	13	61,9	13	61,9	26	61,9	15	71,4	13	59,1	28	65,1
	Total	21	100	21	100	42	100	21	100	22	100	43	100
	p		1						0.52				
VFV													
	before < after	9	42,9	7	33,3	16	38,1	7	33,3	8	36,4	15	34,9
	before>after	12	57,1	14	66,7	26	61,9	14	66,7	14	63,6	28	65,1
	Total	21	100	21	100	42	100	21	100	22	100	43	100
	p		1						0.52				

Pearson Qui-square test.

that protodioscin, an active ingredient of TTerrestris, improve sexual function in women with FSD, due to an increase in levels of total, free and bioavailable testosterone.

The published randomized clinical trials that used TTerrestris, formulated according to the criteria of worldwide standardization, involved a total of 290 women with loss of libido (Gama et al., 2014, De Souza et al., 2016, Postigo et al., 2016, Vale et al., 2018). The trials administered the drug orally, with a 250 mg formulation 3 times a day for 90 to 120 days. As we currently have TTerrestris available in Brazil in the 94mg formulation (3 times a day) and the 280mg formulation (once a day), we chose to compare these two presentations. In male, Kamenov, Fileva, Kalinov, and Jannini (2017) evaluated the effectiveness and safety of TTerrestris in patients with sexual dysfunction and described a significant improvement after comparing with placebo.

We used the FSFI questionnaire as it was designed to address the multidimensional nature of female sexual function (Abdo, 2006; Gerstenberger et al., 2017; Rosen et al., 2000; Woodard & Diamond, 2009). No difference was observed in the FSFI scores between the groups before treatment, 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. The significant improvement in the total mean FSFI scores after the use of TTerrestris observed in premenopausal women are similar to the results described previously (Akhtari et al., 2014; Gama et al., 2014; Vale et al., 2018). When we analyzed all domains separately, we observed an improvement in all but "sexual satisfaction" in the TT3 group. We also observed a significant improvement in the total mean FSFI scores after the use of TTerrestris observed in postmenopausal women and the results were similar to the described previously by our group (De Souza et al., 2016).

We also used the QS-F questionnaire, a tool designed to assess sexual function of Brazilian women (Abdo, 2006). Similarly to what was observed with the FSFI scores, no difference was observed in the QS-F scores between the groups before treatment, confirming that both groups were homogeneous. All women, in both reproductive groups, showed a significant improvement in the total mean QS-F score. In both groups of patients this result was similar to the previously published (De Souza et al., 2016; Postigo et al., 2016; Vale et al., 2018). However, patients in the premenopausal TT3 group did not experienced improvement in the "desire" and "orgasm" domains, and in the TT1 group did not showed improvement in the "pain" domains. For the postmenopausal patients, an improvement was observed in all sexual domains, except for "orgasm" in the TT1 group.

We observed that serum levels of total, free and bioavailable testosterone had a significant increase in all women included in the study, after treatment. These results are in accordance to the previously described by our group, as we described a significant increase in the serum levels of free and bioavailable Testosterone after treatment with TTerrestris 750 mg/day for 120 days (De Souza et al., 2016; Vale et al., 2018). This increase might explain the improvement in the sexual function as Testosterone is important in the normative function of sexual response. It has important action on the central nervous system in the activation of sexual desire and on vaginal trophism boosting genital arousal and lubrication and improves sexual satisfaction (Davis, Davison, Donath, & Bell, 2005; Santi et al., 2018). Moreover, when we compared both dosage regimes of TTerrestris, we did not observe an increase in the testosterone levels in the patients of group TT3, only in those using once a day (TT1) in both reproductive phases. Therefore, when comparing the two dosage regimes, we observed that the use of TTerrestris once a day enabled a higher impact on Testosterone levels, which may also have had an impact on the results observed for the FSFI and QS-F analysis.A possible hypothesis to explain the reason TTerrestris, given once a day, was more effective, than 3 times a day, is that the protodioscin in a single and higher dose could promote a higher LH peak and therefore, an increased testosterone secretion by the ovaries. Moreover, TTerrestris in a single and higher dose could also simulate an increased 5-α-reductase action, converting testosterone into its active form of dehydrotestosterone.

The clitoris is an important organ that, when stimulated, is responsible for providing an orgasmic response. The presence of nitric oxide (NO) isoforms in the human clitoris has already been demonstrated (Adaikan et al., 2000; Sahin et al., 2016; Semerdjieva & Zheljazkov, 2019). However, our results demonstrated a lack of change in the Pulsatility Index of the clitoral artery after the use of TTerrestris confirming that the observed improvement in sexual function, must have been through central mechanisms and increased Testosterone rather than clitoral mechanisms and increased NO.

Sahin et al.. (2016) evaluated the effects of TTerrestris compared with placebo and sidenafil on sexual function. The study showed that TTerrestris is an enhancer of sexual function and behavior by increasing testosterone levels and regulating NO pathways in male rats. Based on this knowledge, we studied the effects of TTerrestris on the clitoral blood flow in women with FSD using color power Doppler ultrasound. The observed values of PI and VFV before treatment, in postmenopausal women, are similar to the described by Alatas and Yagci (2004). To the best of our knowledge, this is the first study to examine the effects do TTerrestris on clitoral artery blood flow in pre and postmenopausal women. Although we did not observe any difference in the PI after the use of TTerrestris in all patients, when we analyzed the Vascular Flow Velocity, we identified a significant reduction in postmenopausal women. This reduction observed in postmenopausal and not in premenopausal women might have occurred as advancing age is associated with structural and functional vascular alterations, resulting in increased vascular stiffness and endothelial dysfunction (Maseroli et al., 2016, Xu, Wang, & Ren, 2017).

The lack of a control group might be considered a limitation of our study, however, previous studies have already demonstrated significant improvements of TTerrestris when compared to placebo. Therefore, the main objective of our study was not to confirm previous studies but to compare different dosage regimes of TTerrestris. Another limitation of our study was the

impossibility of using the new tool for the evaluation of the orgasmic experience in the female population, the F-Orgasmometer. We believe that further studies can use this tool in order for confirm our results.

Conclusion

In conclusion, our study suggests that *Tribulus terrestris* is an effective alternative for the treatment of pre and postmenopausal women with FSD, probably through a mechanism leading to an increase in the serum levels of testosterone. For postmenopausal women it may also improve clitoral artery blood flow. Moreover, the use of 280 mg, once a day seem to have a better effect than the fractional dose administered 3 times a day.

Disclosure statement

There is no conflict of interest among authors of this study.

Data availability statement

The data set of this study will be available by the corresponding author upon request.

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