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Is Tribulus Terrestris Effective at Increasing Sexual Desire in Adult Women Suffering from Hypoactive Sexual Desire Disorder?

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A SELECTIVE EVIDENCE-BASED MEDICINE REVIEW

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ABSTRACT

Objective: The objective of this selective evidence-based medicine (EBM) review is to determine whether or not Tribulus terrestris is effective at increasing sexual desire in adult women suffering from hypoactive sexual desire disorder (HSDD).

Study Design: Review of three randomized controlled trials published in 2014, 2016, and 2017; selection was based on their relevance to the clinical question and on their patient-oriented outcomes.

Data Sources: Three peer-reviewed primary studies comparing the use of Tribulus terrestris to placebo in the treatment of HSDD were found on PubMed.

Outcome(s) Measured: For each trial, patients were divided into either Tribulus terrestris treatment or placebo treatment groups. Trials assessed female sexual function index (FSFI) and sexual quotient female (QS-F) questionnaire score improvements to evaluate treatment efficacy.

Results: All three trials used the FSFI questionnaire and reported a statistically significant ($P < 0.05$) increase in mean change from baseline in sexual desire when using Tribulus terrestris. De Souza et al. and Vale et al. also reported a statistically significant ($P < 0.05$) increase in mean change from baseline of the placebo group of < 0.01 and 0.001, respectively. De Souza et al. and Vale et al. reported a statistically significant ($P < 0.05$) increase in sexual desire using QS-F results with a number needed to treat (NNT) of 20 and 4, respectively.

Conclusion: Tribulus terrestris may safely and effectively improve sexual desire in women with HSDD; however, clear and concise methods and statistical analysis are needed to further investigate its full clinical potential.

Key Words: Hypoactive sexual desire disorder, Tribulus terrestris, female sexual dysfunction

Introduction:

Sexual dysfunction is a worldwide disease burden that affects many individuals, with significant accomplishments made thus far in the treatment, diagnosis, and pathophysiology of male erectile dysfunction, premature ejaculation, and testosterone deficiency syndrome. However, medical treatment and diagnosis of female sexual dysfunction to date still lag behind those of their male counterparts, with emphasis placed on difficulty understanding the female sexual response. The most prevalent sexual disorder affecting women is hypoactive sexual desire disorder (HSDD), defined as a persistent dysfunction in desire and fantasy to engage in sexual behaviors that leads to interpersonal distress not better explained by another condition.[1] Distresses may include declines in self-esteem, mental health, and emotional role fulfillment.

The sexual response is generally divided into four phases: desire, arousal, orgasm, and resolution. Unfortunately, this model does not hold consistently true for all women because of the multifactorial hormonal, neuronal, and psychosocial interactions that motivate female sexual response. The biology of desire is poorly understood in women, but it is hypothesized that HSDD is caused by some maladaptive neuronal process that precludes psychological priming for sex.[2]

HSDD affects approximately 10% of all adult women, although the annual incidence and total healthcare cost of women seeking care for HSDD each year are currently unknown.[3] However, from a 1998-2006 data analysis we do know women with HSDD international classification of disease (ICD) diagnosis generally had higher healthcare expenditures compared to those undiagnosed.[3] Historically, women perceive more barriers to accessing healthcare for sexual difficulties for a number of reasons, including cultural/societal norms, provider-based knowledge, and personal embarrassment.[4] In a survey conducted in 2009 with 3,239 women, only 34.5% had reported a sexual problem to their healthcare provider.[4] HSDD is classified in the

Diagnostic and Statistical Manual of Mental Disorders (5th ed.; *DSM-5;* American Psychiatric Association, 2013) as part of Female Interest/Arousal Desire with diagnosis made on lack of interest and arousal; however, no set analysis criteria or algorithm guides diagnosis and treatment. This diagnostic ambiguity further promotes a lack of confidence in the healthcare system and compounds the under-recognized healthcare-seeking and diagnostic behavior of women with HSDD.

Current treatment options for women with HSDD include both pharmacotherapy and psychotherapy. As of 2015, flibanserin was the only medication approved by the Food and Drug Administration (FDA) for treating HSDD in perimenopausal women. Some off-label pharmacological medications indicated for treatment are bupropion, sildenafil, buspirone, esterified estrogen/methyltesterone, and testosterone transdermal patches.[1] Psychotherapy options include cognitive behavioral therapy, sensate focus, mindfulness training, and bibliotherapy.[1] While all of these treatments may have shown beneficial effects for women at one point, they have not been widely accepted in the clinical management of patients with HSDD.

Herbal supplements have long been used in various cultures to treat and cure diseases. Tribulus terrestris is a plant native to Asia, Europe, and Africa and has long been endorsed culturally for its possible aphrodisiac properties. Recent studies propose some validity to its ability to mimic sex hormones for a natural option for women. The aim of this paper is to evaluate the efficacy of Tribulus terrestris in increasing sexual desire in adult women older than 18 years of age with HSDD by way of analyzing three double-blind randomized control trials.

Objective:

The objective of this selective evidence-based medicine (EBM) review is to determine whether Tribulus terrestris is effective at increasing sexual desire in adult women suffering from HSDD.

Methods:

All three articles were researched using PubMed and were selected based on relevance to the clinical question and their patient-oriented outcomes. The key words used to identify literature included hypoactive sexual desire disorder, female sexual dysfunction, and Tribulus terrestris.

Three double-blind randomized placebo-controlled clinical trials were used in this systematic review. All three studies required a population of adult women older than 18 years of age with reported diminished libido. Table 1 displays the key characteristics and demographics of the included studies. The intervention administered Tribulus terrestris orally to the experimental group and a visually equivalent placebo to the control group. The outcome measured was improvement in sexual desire. The statistics that were used and reported in all three studies were mean changes from baseline, *P* values, ANOVA test, Wilcoxon test, and McNemar test.

Table 1: Demographics and Characteristics of Included Studies

Study	Type	# Pts	Age	Inclusion Criteria	Exclusion Criteria	W/D	Interventions
Akhtari[5] (2014)	Double Blind RCT	67	36±7 years	Women of childbearing age, having normal breast exam, pelvic exam, negative pap smear, married and actively living with a partner, lack or loss of libido causing distress	Lack of steady sexual partner, serious medical condition, major depression disorder or other psychiatric disorders, history of genital tract or breast cancers, menopause, pregnancy, husband's sexual problems and active plans for divorce	7	Tribulus terrestris extract 7.5mg/day
De Souza KZ[6] (2016)	Prospective double-blind RCT	45	43-65 years	Age between 1-10 yrs since last menstrual period, FSH	Used hormone or drugs within previous year, smokers, had HTN,	9	Tribulus terrestris 250 mg TID orally

				level > 30, estradiol level < 40, body mass index less than 28	collagenosis, unbalanced endocrine system, pulmonary, renal, hepatic, vascular, thromboembolic disease, history of endometrial cancer, MI, oophorectomy, partner with sexual problems, interpersonal relationship problems		
Vale[7] (2017)	Double blind RCT	64	18-44 years	Stable relationship for 2 yrs, regular menstrual cycles, diminished libido	Pregnant, on hormonal contraception, regular/medications, clinically depressed, had HTN, collagenosis, unbalanced endocrine system, pulmonary, renal, hepatic, vascular, thromboembolic disease, history of endometrial cancer, MI, partner with sexual problems, interpersonal relationship problems	24	Tribulus terrestris 250 mg TID orally

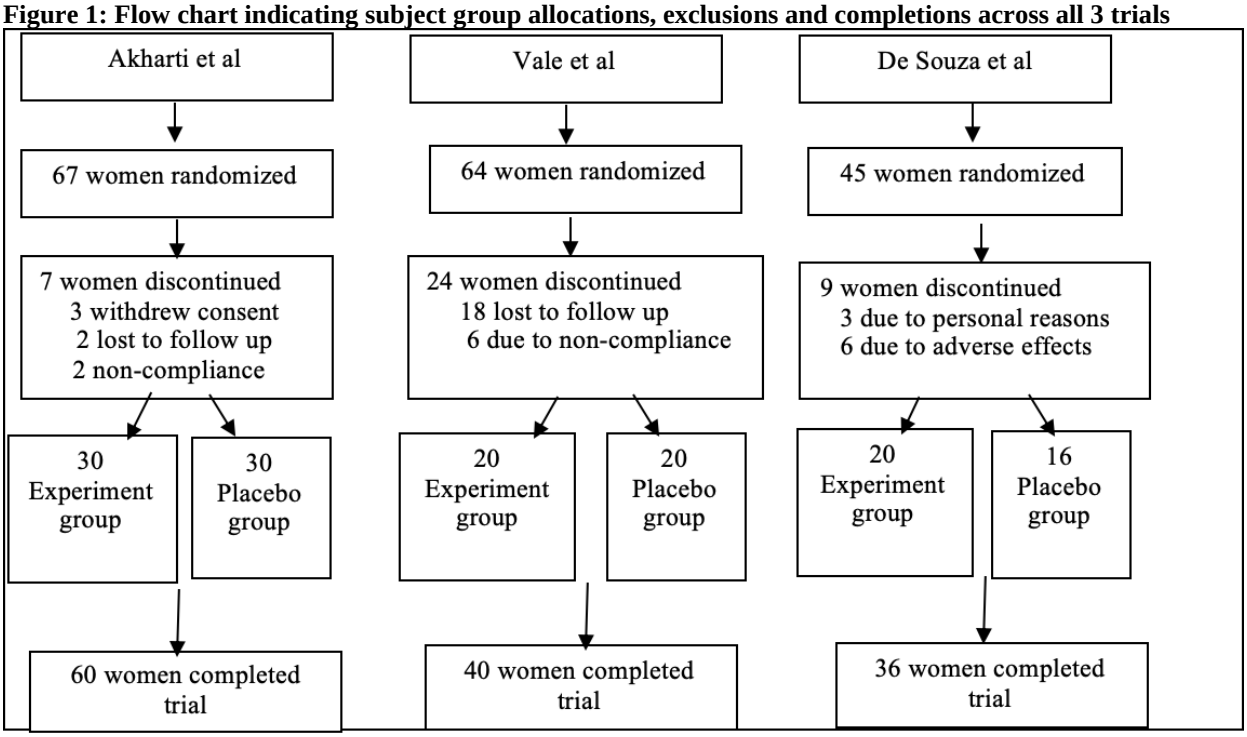
Outcomes Measured:

All three articles used the Female Sexual Function Index (FSFI) questionnaire to assess the efficacy of Tribulus terrestris therapy in improving sexual desire. The FSFI questionnaire assesses 6 domains of female sexual function: desire, arousal, lubrication, orgasm, satisfaction, and pain. Vale et al. and de Souza et al. used an additional questionnaire, the sexual quotient female (QS-F) questionnaire, which includes 5 domains: desire, arousal/lubrication, orgasm, pain, and satisfaction. Both surveys use Likert-type response formats and are scored from 0 to 5. Low scores from both questionnaires indicate severe female sexual dysfunction.

Results:

Akhatri et al. selected 67 adult women of whom 33 were randomly assigned to the experimental group and 34 to the control group. Of the 67 women, a total of 7 discontinued the trial because of noncompliance, loss to follow up, or withdrawn consent.[5] The randomized study was conducted in two medical centers in the Tehran Province of Iran. De Souza et al. selected 45 women for their study from which 9 were excluded: 3 withdrew because of personal reasons and 6 as a result of adverse side effects from taking the medication. This study was conducted in the Clinic of Sexology of the Department of Gynecology and Obstetrics in Brazil. Vale et al. selected 64 women from which 24 were excluded from the study because of noncompliance or loss to follow up. This study was conducted at the Universidade Federal de Minas Gerais in Brazil. None of the excluded patients were used in the final analysis across all trials. Figure 1 illustrates subject group allocations, exclusions, and completions across all 3 trials.

Figure 1: Flow chart indicating subject group allocations, exclusions and completions across all 3 trials



All three trials used the FSFI questionnaire and reported a statistically significant ($P < 0.05$) increase in mean change from baseline in sexual desire when using Tribulus terrestris. De Souza et al. and Vale et al. also reported a statistically significant ($P < 0.05$) increase in mean change from baseline of the placebo group of <0.01 and 0.001 respectively. The results are illustrated in Table 2. Data from these trials using FSFI as an outcome measure were reported as continuous data that could not be converted to dichotomous form to further evaluate efficacy of treatment. Vale et al. and de Souza et al. noted no statistically significant difference in the FSFI scores between groups before treatment, with P values > 0.1 validating homogeneity. Akharti et al. did not report on any statistical significance between groups on the FSFI before treatment.

Table 2: Efficacy of Tribulus terrestris in improving sexual desire using FSFI within groups

Study	Tribulus terrestris mean change from baseline	Placebo Mean change from baseline	P value*	P value**
Akhtari et al.	.84	.2	< 0.0001[+]	N/A
De Souza et al.	1.6	1.2	<0.01	<0.01
Vale et al.	1.59	1.14	<0.001	0.001

*p value of Tribulus terrestris pre and post treatment with no variance accountability
**p value of placebo pre and post treatment with no variance accountability
+variance between the two groups are accounted

Using QS-F, both de Souza et al. and Vale et al. reported a statistically significant ($P < 0.05$) increase in sexual desire. Vale et al. reported a QS-F score in the desire domain that showed 70% of women who were taking Tribulus terrestris compared to 65% of women taking placebo felt an improvement in desire, for a number needed to treat (NNT) of 20.[7] A NNT of 20 means that for every 20 women treated with Tribulus terrestris, one more person will achieve the desired outcome compared to those taking the placebo. De Souza et al. trial reported a QS-F score in the desire domain that showed 75% of women who were taking Tribulus terrestris compared to 50% of women taking placebo felt an improvement in desire, for a NNT of 4.[6] The results for QS-F are shown in Table 3.

Table 3: Efficacy of Tribulus terrestris in the treatment of HSDD using QS-F

Study	CER	EER	RRI	ARI	NNT	P value
Vale et al	0.65	0.70	0.08	0.05	20	<0.01
De Souz et al	0.50	0.75	0.50	0.25	4	0.01

One adverse effect of abdominal cramping was reported in the Akhatri et al. study; however, the group was not specified. Vale et al. did not report any side effects using the drug or placebo within the respective groups. De Souza et al. reported nausea as a side effect, with 6 women withdrawing, 3 from the placebo group and 3 from the experimental group. Compliance of the participants was not noted in the studies conducted by Vale et al. and de Souza et al. over the 120-day duration of the trials.[6,7] The study conducted by Ahkatri et al. reported that participants were followed for 2 consecutive months with 3 in-person visits throughout the length of the 4-week study.

Discussion

Flibanserin is the only drug approved by the FDA for treating HSDD for perimenopausal women; therefore, in the absence of treatment options, homeopathic products offer alternative therapy. Since flibanserin was approved only for perimenopausal women in the United States, its application to all women is limited, and some associated side effects, such as somnolence, dizziness, and insomnia, exist. All of the noted side effects are significant, as they could interfere with its intended use of initiating and increasing sexually satisfying events.

Using three double-blind randomized controlled trials, this selective systematic analysis reviewed the safety and efficacy of Tribulus terrestris in improving the sexual desire in women with HSDD older than 18 years of age. Exclusion criteria were exhaustive and included both medical and psychological conditions, medications, and other sexual dysfunctions in addition to

HSDD. All three trials using the FSFI and QS-F questionnaires showed that in these women with HSDD, taking Tribulus terrestris was associated with a statistically significant increase in sexual desire. While the FSFI is a well-accepted questionnaire vetted to assess female dysfunction and is used in numerous trials, including those that led to the FDA approval of flibanserin, QS-F is not. QS-F was developed to specifically assess female sexual dysfunction in Brazilian women. Therefore, the extent to which this questionnaire can be used in the United States as a treatment outcome would need further evaluation. Also, no *P* values were reported in the Vale et al. and de Souza et al. studies between the treatment and placebo groups before and after treatment that adjusted for variance to further solidify the statistical significance of the treatment intervention.

All three studies varied in the population studied, manufacturers used, compliance surveillance, length of drug administration, and intervention formulations. All studies were conducted outside the United States in countries with different attitudes toward sexual health. Akharti et al. noted that Iranian women tend to be more reserved in their sexual beliefs because of their conservative culture, leading to over- or underestimations in sexual desire.[5] Akhatri et al. used a syrup formulation of Tribulus terrestris over 4 weeks while Vale et al. and de Souza et al. used tablets and assessed over 120 days. Therefore, from the three studies, therapeutic treatment lengths and formulations were not evaluated and may have contributed to the variations in outcomes although all studies showed benefits.

The FDA does not regulate alternative products, such as herbal or nutritional supplements, thus limiting the number of available studies undergoing rigorous scientific compliance when measuring objective patient outcomes. Moreover, the exact mechanism of the effect of Tribulus terrestris on increasing sexual desire is not well understood, creating another hurdle in the number of clinical trials available. From the lower NNT of 4 obtained in the De Souza et al. study compared to the Vale et al. study of 20 some inferences can be made on the possible effect of Tribulus terrestris on hormones since the two study groups mainly differed in post and premenopausal women. Postmenopausal women naturally undergo significant hormonal

changes. The worldwide use of herbs is increasing; therefore, women will have no problems obtaining this supplement from the market. Healthcare providers will inevitably encounter women in the primary-care or gynecological setting seeking advice on herbal supplements for HSDD.

Conclusion:

Tribulus terrestris may safely and effectively improve sexual desire in women with HSDD; however, clear and concise methods and statistical analysis are needed to further investigate its full clinical potential. The studies conducted by Vale et al and de Souza et al could have taken data a step further to assess the true statistical significance of Tribulus terrestris intervention before and after treatment compared to the placebo group after matching for effective variance. No serious or life-threatening adverse reactions were reported. However, research is needed in the United States with clearly defined and vetted patient outcome measurements appropriate for the culture of the population. Studies using diary documentations for compliance and sexually satisfying events as part of the measured outcome would also add great value to further research methods. Tribulus terrestris production quality standardization is another area that if included in future studies will help to increase confidence in its efficacy.

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