Original Article

Comparison of the effect of Elaeagnus angustifolia flower capsule and sildenafil citrate tablet female sexual interest/arousal disorder in clinical trial study

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Abstract

Background and Aims: Sexual desire is one of the main issues affecting people's individual and social life. The present study aimed to compare the effects of Elaeagnus angustifolia extract and sildenafil citrate tablet on female sexual interest/arousal disorder (FSIAD) among the women referring to health centers in 2013. **Methods:** In this randomized clinical trial, 125 women between 18 and 40 years old who suffered from FSIAD were divided into Elaeagnus angustifolia, sildenafil citrate, and control groups. The study data were gathered using Female Sexual Function Index (FSFI) and through measurement of TSH and prolactin. The first intervention group had to consume 4.5 g Elaeagnus angustifolia in two divided doses for 35 days and the second one had to use 50 mg sildenafil citrate tablets for 4 weeks one hour before their sexual relationships. On the other hand, the control group was required to consume the placebo. The data were analyzed using the SPSS statistical software (v. 18) and $P < 0.05$ was considered as statistically significant. **Results:** The frequency of sexual interest/arousal before the intervention was 53.7%, 50. %, and 66.7% in the Elaeagnus angustifolia, sildenafil citrate, and control groups, respectively ($P = 0.269$). However, these measures were respectively obtained as 19.5%, 33.3%, and 52.4% after the intervention ($P = 0.007$). **Conclusion:** Both interventions were effective in improvement of sexual interest/arousal. Yet, further studies are required to be conducted on the issue. Therefore, direct examination of health care providers, identifying and diagnosing sexual problems are the most important primary care.
Influences the process of couples' sexual problems.

Keywords: Elaeagnus angustifolia, sexual interest/arousal, sildenafil citrate

Introduction

Healthy sexual function is one of the main factors affecting women's welfare and life quality.[1] Researches have shown that more than 40% of women experience sexual problems and 12% of these women are distressed due to their problems.[2] In spite of the fact that sexual disorders are widely being discussed through the recent years, neither women nor caregivers freely talk about this issue during clinical visits. This might be in contrast to the high prevalence of sexual disorders among women.[3] In general, women may get upset by talking to their physicians about their

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sexual concerns because of time limitation, lack of appropriate treatment for women, and their shyness.[4] While primary care surveys have shown that less than 50 percent of physicians ask their patients about sexual activity and related concerns. Understanding normal sexual responses and evaluating and treating sexual dysfunction requires comprehensive gynecological care.[5] Therefore, physicians should start discussing sexual function during the clinical visits and consider evaluation of patients' sexual function as a priority.

One of the factors leading to sexual dysfunction is related to sexual desire disorders. According to global statistics, problems associated with sexual desire, particularly reduction of sexual desire, are the most common sexual complaint among women.[6,7] Based on DSM-IV TR, reduction of sexual desire is defined as chronic or recurrent reduction or lack of sexual fantasy, thoughts, or desire and acceptance of sexual activity.[2] In one study 39%, 35%, 22%, and 12.8% of the subjects reported orgasm disorder, arousal disorder, HSDD, and pain during intercourse, respectively.[8] Similarly, Frank *et al.* (2008) reported the prevalence rate of sexual disorders to be 40% and that reduction of sexual desire existed in 10-46% of the cases.[9] Furthermore, Song *et al.* asked 47,000 young Korean women to take part in a web-based study in order to investigate the prevalence of female sexual dysfunction. Overall, 504 women with the mean age of 28.5 years (range: 18-52 years) were assessed. According to the results, 44%, 49%, 32%, 37% and 34.6% of the participants complained about reduction of sexual desire, arousal problems, orgasm disorders, lack of sexual satisfaction, and pain during intercourse, respectively.[10] One study in Iran also showed that 39% of the study population did not have pleasurable feelings during their sexual activity and 10.5% had never experienced orgasm.[11]

One of the most important factors of happiness in marital life is having enjoyable sex, adjustment, and marital satisfaction in which the husband and wife often feel happy and satisfied with each other. This satisfaction is created through mutual interest, caring for one another, accepting, understanding each other, and satisfying one's needs, including sexual need.[12,13] In one study, being unsatisfied leads to deprivation, failure, and lack of security in couples.[14] Research has also highlighted the importance of the impact of marital satisfaction on a wide variety of clinical outcomes such as mental health, physical health, job satisfaction, and even employment.[15]

Considering the high prevalence of sexual dysfunction, with HSDD being the most common one among women, strategies are required to eliminate or reduce these problems. These strategies may include education, individual consultation, couple therapy, sex therapy, hormone replacement therapy (e.g. tibolone or exogenous testosterone replacement), and synthetic steroid estrogen, progesterone, and androgen (particularly for menopausal women). Also, centrally acting agents can have a positive impact on sexual function by inhibition of serotonergic activity, facilitation of dopaminergic activity, or attachment with melanocyte receptors. However, no pharmacological treatment has been approved by Food and Drug Administration (FDA) for treating female sexual dysfunction. To date, androgens and Phosphodiesterase type 5 (PED5) inhibitors are two strategies employed for reduction of sexual disorders in women.[16] A pharmacodynamic study in healthy women indicated that sildenafil citrate increased vaginal blood flow in response to sexual arousal.[17] Sildenafil citrate was also effective in increasing sexual arousal in the menopausal women suffering from Female Sexual Arousal Disorder (FSAD).[18] However, some studies have not confirmed the effectiveness of this drug on female sexual dysfunction.[19]

Considering World Health Organization's (WHO) approach to traditional medicine, attempts should be made to find strategies for improvement of female sexual dysfunction in different schools of medicine. One of these schools is the dynamic Iranian traditional medicine.

Elaeagnacea is one of Elaeagnus angustifolia plant families which is of great importance in traditional medicine. Elaeagnacea exists in north Asia to the Himalayas and Europe and its various species are used as treatment agents which has been investigated in several studies.[20-26] For instance, Also, this plant's leaves are used for treatment of asthma, bronchitis, and other respiratory diseases in Chinese traditional medicine.[20] Elaeagnus angustifolia is frequently used in Iranian traditional medicine and various treatment properties have been mentioned for its fruit, gum, and leaves. It has been stated to have analgesic and anti-inflammatory properties and can be used for treatment of rheumatoid arthritis. In addition, decoction and extract of its fruit can be employed for treatment of fever, jaundice, asthma, tetanus, and rheumatoid arthritis.[20-23] The previous studies have revealed that fruit and leaves of Elaeagnus angustifolia contained a considerable amount of flavonoid compounds, terpenoid compounds, cardiac glycosides, sitosterol, and carvacrol.[20,25,26] Evidence has shown that some flavonoid compounds and sitosterol have analgesic and anti-inflammatory properties.[27] Moreover, a study investigated the effects of water and alcohol extracts of Elaeagnus angustifolia fruit on mice's intestinal smooth muscles relaxation and demonstrated that the flavonoids in this fruit played a role in smooth muscles relaxation.[22] In traditional medicine, various plants such as ginseng, yohimbine, rose flower extract and Elaeagnus angustifolia are used for treatment of sexual dysfunction. Elaeagnus angustifolia flower is one of the herbal medications which, according to the specialists in traditional medicine, is hot and dry, is aromatic, and can stimulate sexuality especially in young girls and women.[28] Basically, the types of women's sexual dysfunction and related factors are less studied in the Middle East.[29,30] Besides, Although Elaeagnus angustifolia has been highly recommended to be used in Iranian traditional medicine, but little studies have been conducted in this area up to now.[31,32] Therefore, the present study aims to compare the effects of Elaeagnus angustifolia capsule and sildenafil citrate tablet on HSDD in women referring to the selected health centers affiliated to Shiraz University of Medical Sciences, Shiraz, Iran.

Methods

This study was a randomized clinical trial and was approved by the local Ethics Committee of Shiraz University of Medical Science. Based on the study objectives and the previous studies conducted on the issue,[19,33,34] considering error rate of 5%, power of 80%, minimum mean difference of 0.6, and variance of 0.92, a 72-subject sample size was computed for the study using the following formula:

$$n = \frac{(2z_{1-\alpha/2} + z_{1-\beta})\delta^2}{d^2}$$

However, considering the loss rate of 10% and the following formula, an 84-subject sample size (42 subjects in each group) was determined for the study.

$$n' = n \times \frac{1}{1-p}$$

Overall, out of the 140 qualified women entered into the study, 125 ones (41 in the Elaeagnus angustifolia group, 42 in the sildenafil citrate group, and 42 in the control group) completed the study [Figure 1]. The study population included the 18-40 year old women suffering from sexual dysfunction who had referred to the selected clinics which were covered by Enghelab health center, Shiraz, Iran. The inclusion criteria of the study were obtaining scores <22 in Female Sexual Function Index (FSFI), not being pregnant, not breastfeeding, not having the history of heart attack, hypertension, and cardiovascular diseases, not consuming the medications affecting sexual function such as common antidepressants, not suffering from dyspareunia or vaginismus, not having the history of different types of headaches such as migraine, not using hormone drugs particularly oral contraceptive pills and lack of drug or alcohol abuse.

The study data were collected through demographic information form, FSFI, and measurement of TSH and prolactin. FSFI which contains 19 items evaluates females' sexual function in 6 domains of sexual desire, arousal, lubrication, orgasm, satisfaction, and pain. The study women were required to answer the questions according to their sexual desire and function during the past 4 weeks. In general, obtaining scores <28 is considered as sexual dysfunction. Nevertheless, since assessment of pain (6 points) was omitted from the present study, score of 22 was considered instead of 28. The reliability and validity of the Persian version of FSFI were determined by Mohammadi *et al.* in 2008. The reliability of the whole questionnaire and the subscales was confirmed by Cronbach's alpha >0.70. Moreover, investigation of the validity of the Persian version of this questionnaire indicated a significant difference between the total mean score and the mean scores of the subscales in the two groups ($P < 0.001$).[35,36]

After obtaining written informed consents, TSH and prolactin were assessed in all the study participants in order to reject

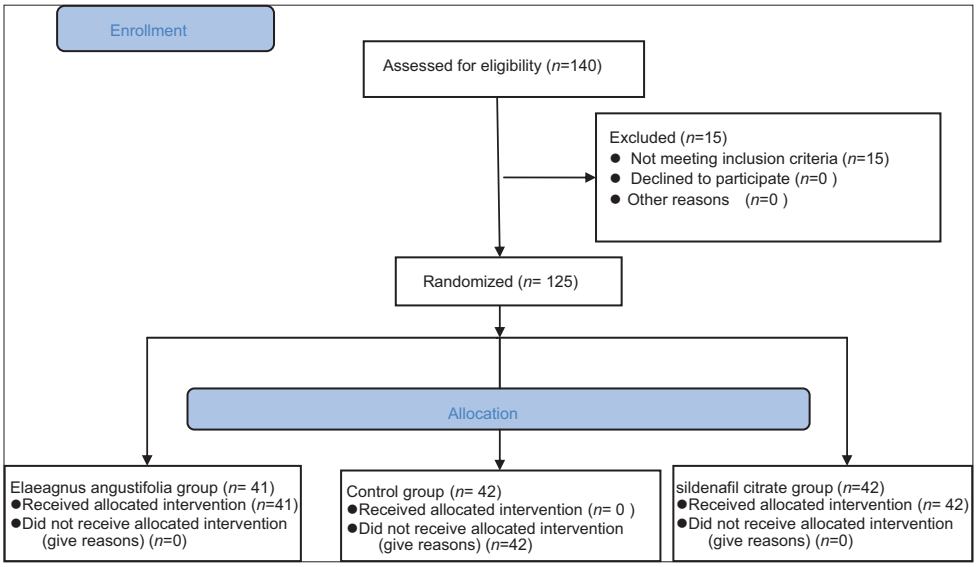

Figure 1: CONSORT Diagram

Table 1: Comparison of frequency of marriage age between the intervention and control groups

Marriage age	Elaeagnus angustifolia flower capsule group		Sildenafil Citrate group		Control group		Total		*P*
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	
20<	19	46.3	16	38.1	20	47.6	55	44	0.308
20-25	13	31.7	20	47.6	11	26.2	44	35.2	
26-30	6	14.6	6	14.6	9	21.4	21	16.8	
30>	3	7.3	0	0	2	4.8	5	4	

thyroid and prolactin disorders which are the secondary causes of sexual dysfunction.

In this study, the samples were selected through convenience sampling and were randomly allocated into two intervention groups and a control group. The first intervention group had to consume 4.5 g Elaeagnus angustifolia in two divided doses (2 capsules every 12 hours) for 35 days and the second one had to use 50 mg sildenafil citrate tablets for 4 weeks. The subjects had to consume their medications one hour before their sexual relationships. They were also required to continue using the medications during their menstrual cycles. The control group received the placebo which they were required to consume for 35 days (2 tablets every 12 hours). The study participants were followed up twice a week through SMS and once a week through phone contact. After the intervention, the study women completed FSFI.

Statistical analysis

After all, the data were entered into the SPSS statistical software (v. 18) and were analyzed using paired *t*-test, one-way ANOVA, and post-hoc Bonferroni tests. Besides, $P < 0.05$ was considered as statistically significant.

Results

The mean age of the study women was 32.67 + 5.05 years and the highest frequency was related to 30-40 years age group (67.2%). In addition, the mean age of the participants' husbands was 37.7 + 6.51 years. Besides, the mean length of marriage was 21.59 + 4.61 years with the highest frequency being related to below 20 years old age group (44%) [Table 1].

The results of independent t-test revealed no significant difference among the three groups regarding TSH ($P = 0.448$) and prolactin levels ($P = 0.179$) before the intervention. Moreover, the frequency of HSDD was 53.7%, 50%, and 66.7% in the Elaeagnus angustifolia, sildenafil citrate, and control group, respectively, before the intervention. Also, the total frequency of HSDD was 56.8% before the intervention. According to the results of Chi-square test, the difference among the three groups was not statistically significant before the intervention ($P = 0.269$), while a significant difference was found among the three groups in this regard after the intervention ($P = 0.007$) [Table 2]. Based on the results of McNemar test, a significant difference was observed in the Elaeagnus angustifolia group before and after the intervention ($P = 0.001$). However, no significant difference was found in the sildenafil citrate group ($P = 0.039$) and the control group ($P = 0.109$) before and after the intervention. Overall, Elaeagnus angustifolia and sildenafil citrate groups respectively showed 63.3% and 33.33% reduction of changes compared to before the intervention.

Least Significant Difference (LSD) test was used for two-by-two comparison of the study groups. Accordingly, a significant difference was found between Elaeagnus angustifolia and control groups ($P < 0.001$) as well as between sildenafil citrate and control groups ($P = 0.001$) regarding sexual desire [Table 3].

Discussion

During the past years, great advances have been made in recognition and treatment of sexual dysfunction in women. Some treatment methods, such as testosterone, have also been entered into the pharmaceutical market. The present study compared the effects of Elaeagnus angustifolia capsule and sildenafil citrate tablet on HSDD and revealed the effectiveness of both interventions in increasing the patients' sexual desire.

In this study, the three groups' means of TSH and prolactin levels were within the normal limits before the intervention. Hyperprolactinemia is a common hormonal disorder in women which may lead to sexual dysfunction. Kadioglu *et al.* (2005) investigated sexual function in the patients suffering from hyperprolactinemia and reported FSFI total score to be 23.4 in the patients and 1.31 in the healthy women ($P < 0.001$).[37]

After the intervention in the present study, the frequency of HSDD reduced from 53.7 to 19.5 in the Elaeagnus angustifolia

Table 2: Comparison of frequency of sexual dysfunction (desire area) before and after intervention between the intervention and control groups

Areas of sexual function (desire)	Elaeagnus angustifolia flower capsule group		Sildenafil Citrate group		Control group		total		*P*
	Number	Percent	Number	Percent	Number	Percent	Number	Percent	
Before intervention	22	53.1	21	50	28	66.7	71	56.8	0.269
After intervention	8	19.5	14	33.3	22	52.4	44	35.2	0.007
P	0.001		0.039		0.109				

Table 3: Comparison of average score of sexual dysfunction (in desire area) before and after intervention between the tests and control groups

Areas of sexual function		Elaeagnus angustifolia flower capsule group	Sildenafil Citrate group	Control group	*P*
desire	Before intervention	2.98±0.99	3.15±0.94	2.78±0.88	0.201
	After intervention	3.79±0.86	3.51±0.88	2.97±1.01	<0.001
	P	<0.001	0.001	0.208	

group (P = 0.001) and from 50 to 33.3 in the sildenafil citrate group (P = 0.039). Berman *et al.* (2001) in their double-blind placebo-controlled clinical trial investigated the effect of sildenafil citrate (25-100 mg, one hour before intercourse) in 202 menopausal women suffering from FSAD after hysterectomy in a 12-week period. The study results showed that sildenafil citrate was more effective than the placebo in the women with FSAD without HSDD (P < 0.02), but not considerably effective in those suffering from both FSAD and HSDD.[38] Later on, Berman *et al.* (2003) conducted a 12-week controlled study and treated 202 menopausal women suffering from FSAD by sildenafil citrate (50 mg adjustable up to 25-100 mg). In that study, the data were collected using Female Intervention Efficacy Index (FIEI) and Sexual Function Questionnaire (SFQ). The results indicated a significant improvement in sexual arousal (P = 0.017) and sexual satisfaction (P = 0.015) compared to the control group. However, no significant improvement was observed in sexual desire.[18] These results were in contrast to those of the current study demonstrating the effectiveness of sildenafil citrate in sexual desire (P = 0.039). This might be due to the fact that our study participants were in reproductive ages. During this period, hormonal changes in each cycle provide the ground for showing emotional-behavioral and sexual tendencies. The participants of Berman's study, on the other hand, were menopausal women. Due to severe reduction of female hormones during menopause, such women usually complain about reduction of sexual desire and quality of life. It should also be mentioned that menopause is not a transient period of a disease, but a biological, psycho-social phenomenon which occurs due to increase of age and hormonal changes.[39] Thus, hormonal changes considerably reduce menopausal women's sexual function and result in sexual dysfunction.[40] Additionally, FSFI was used to collect the data in the present study. This instrument separately evaluates various dimensions of sexual function providing the possibility to completely investigate women's sexual function through the sexual cycle. Overall, various studies have demonstrated the effect of menopause on the prevalence of sexual dysfunction. Also, the prevalence of HSDD has been reported to be 16-26% among the women with early menopause and 6.6-9% among those with normal menopause.[41,42]

Furthermore, increase of age and decrease of estrogen level also have a considerable effect on sexual function and can impact all the dimensions of sexual health, including sexual desire.[43] Androgens play a critical role in sexual desire and arousal.[44] As the age increases, circulating androgen level decreases in such a way that its level at the age of 40 is half of that at 20 years of age.[45]

A placebo-controlled study performed in Italy showed that sildenafil citrate could improve sexual function in menopausal women suffering from FSAD,[46] which is in agreement with the findings of the present study. The clinical effectiveness of sildenafil citrate compared to placebo was also confirmed in another large study which was conducted on the women with FSAD.[47]

Up to now, no studies have been conducted on the effect of Elaeagnus angustifolia on sexual disorders. Therefore, the results of the present study were compared to those performed on the effect of other medicinal plants on sexual disorders. Maca root is one of the effective medicinal plants in improvement of sexual desire. This plant is from the brassica family and plays a key role in improvement of women's sexual desire and men's erectile dysfunction.[48] Similarly, Elaeagnus angustifolia improved the sexual desire in the current study. In another study, Ito (2006) used ArginMax (an herbal supplement) in 22-73 year old women with lack of sexual desire. The results of that study indicated a significant improvement in the intervention group's sexual desire compared to the placebo group (72% vs. 47%; P = 0.03).[49] According to studies, herbal medications, such as ArginMax, ginseng, ginkgo biloba, and ethanol extract,[50,51] improved sexual dysfunction through increase of Nitric Oxide (NO) production. NO is also among the compounds derived from Elaeagnus angustifolia flower. Besides, sildenafil citrate is a PDE5 inhibitor which increases the production of NO through catabolism of CGMP. This will eventually lead to relaxation of smooth muscles, particularly in arteries, veins, capillaries, and the clitoris tissue.

To date, Elaeagnus angustifolia has been confirmed to contain several flavonoids, including some flavones such as chrysin, which have a slight antagonist effect on benzodiazepines receptors. These agents might also be the reason for muscle relaxation activities.[22]

Flavonoids in Elaeagnus angustifolia, which too exist in other plants, can lead to endothelium-dependent relaxation of human arteries. Evidence has also confirmed the relaxing effects of flavonoids on rats' uterine smooth muscles and ileum. Flavonoids have shown endothelium-dependent NO-cGMP vascular relaxation, as well.[52] NO as an endogenous venous dilator plays a critical role in vascular tone adjustment.[53] Besides, some animal studies have demonstrated the role of NO in vasodilation through β2-AR receptor.[54,55] Based on the aforementioned reports, the effectiveness of Elaeagnus angustifolia flower might result from the flavonoid compounds which lead to relaxing effects by increasing NO level. NO is also called vasodilator and is found in almost all tissues.[56]

The findings of the present study also demonstrated the effectiveness of Elaeagnus angustifolia flower and sildenafil citrate in improvement of sexual desire. According to the results, a significant difference was observed in the Elaeagnus angustifolia group (P = 0.001) and the sildenafil citrate group (P = 0.039) before and after the intervention, while no significant difference was found in the control group (P = 0.109).

Conclusion

In this study, Elaeagnus angustifolia and sildenafil citrate groups respectively showed 63.3% and 33.33% reduction of changes compared to before the intervention. Thus, these interventions might be safe and effective. Yet, further clinical studies are required to be conducted on the issue.

Ethical considerations

This research project was approved by the local Ethics Committee of Shiraz University of Medical Sciences and written informed consents were obtained from all the participants. The protocol was designed in accordance with the ethical principles of the Helsinki Declaration (World Medical Association, 2002). The patients were given a verbal lecture and written information about the goals and approach of the project, and then they accepted to help the researchers to perform the study. Besides, assured the participants that their information would be kept confidential and no names would be mentioned.

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Conflict of interest

There is no conflict of interest.

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