Original Article

Comparison of *Elaeagnus angustifolia* Extract and Sildenafil Citrate on Female Orgasmic Disorders: A Randomized Clinical Trial

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Abstract

Background: Orgasmic disorder can create a feeling of deprivation and failure and provide mental problems, incompatibility and marital discord. This study aimed to compare the effects of *Elaeagnus angustifolia* flower extract and sildenafil citrate on female orgasmic disorder in women in 2013.

Methods: In this randomized clinical trial, 125 women between 18-40 years old who suffered from orgasmic disorder were divided into three *E. angustifolia*, sildenafil citrate and control groups. The data were gathered using Female Sexual Function Index and through measurement of TSH and prolactin. The first intervention group had to consume 4.5 *gr E. angustifolia* extract 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 relationship. However, the control group had to consume the placebo. The data were analyzed using paired t-test, one-way ANOVA, and Bonferroni post-hoc test and $p<0.05$ was considered significant.

Results: The frequency of orgasmic disorder before the intervention was 41.5%, 40.5%, and 57.1% in *E. angustifolia*, sildenafil citrate, and control groups, respectively ($p=0.23$). However, these measures were respectively 29.3%, 16.7%, and 50% after the intervention ($p=0.004$). A significant difference between the two groups regarding sexual satisfaction after the intervention ($p=0.003$) compared to the beginning of the study ($p=0.356$). Besides, the highest reduction of changes after the intervention (58.82%) was observed in the sildenafil citrate group.

Conclusion: Both *E. angustifolia* extract and sildenafil citrate were effective in reduction of the frequency of orgasmic disorder in women.

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Introduction

Female sexual dysfunction is a serious, common, multifactorial general health problem which is usually neglected in the general population while affecting the women's quality of life to a great extent (1). Lack of sexual health and security will result in anger, excessive rage, depression, drug abuse, lack of physical and psychological capability for parenting and child care, lack of sufficient skills for having a healthy emotional relationship, inability to flourish in the society, infanticide and even death (2). In one study conducted in Hong Kong in 2007, Zhang interviewed 1510 Chinese women who were between 19 and 49 years old and showed that 37.9% of the participants suffered from at least one sexual disorder (3). One other study in Egypt showed the

prevalence of sexual dysfunction to be 76.9% among the studied women, with low sexual desire being the most prevalent one (66.4%). Besides, as the women's age increased, the prevalence of sexual disorders increased, as well (4). One study on Kurdish women in Iran indicated that 77% of the studied participants had one sexual disorder (5). Another study in Iran also revealed that 10.5% of women had never experienced orgasm (6). In the study that Safarinejad (2006) conducted on 20-60 year old women in Iran, the prevalence of low sexual desire, lack of sexual arousal, lack of orgasm, and pain during intercourse was reported as 35%, 30%, 37%, and 26%, respectively (7).

Up to now, most studies regarding the pharmacological treatments for sexual dysfunction have been conducted on males and female sexual dysfunction has been less taken into account (8-10). Recently, pharmacological treatments have been considered for female sexual dysfunction mainly focusing on improvement of androgen deficiency, increase of blood flow to the genital area and stimulation of the central nervous system (11).

Estrogen, progesterone, and testosterone are the main effective hormones in females' sexual response (12). In addition, androgen deficiency is one of the main causes of female sexual dysfunction (13). Thus, these compounds have been used for hormone therapy in some studies. Nonetheless, testosterone has been less welcomed due to its side-effects, including hirsutism and acne (9, 14).

According to some researches, sildenafil citrate is effective in treatment of orgasm as well as arousal disorders and increase of females' sexual experiences (15-18). Sildenafil citrate is among the phosphodiesterase type 5 (PDE5) inhibitors which improve female sexual dysfunction through increasing blood flow to corpus cavernosum of clitoris, vagina and labia minor (15-17,19-25). However, in rare cases, its consumption might be accompanied by complications, such as mild headache, urinary tract infection and nausea (14).

Complementary and Alternative Medication (CAM) is also used in treatment of sexual disorders (26). Ginseng which is a Chinese traditional medication is one of the effective herbal medicines in treatment of sexual disorders (27-28). Other common medications include Yohimibine and Ginkgo biloba. However, Yohimibine has been shown to be more effective in treatment of sexual dysfunction in males as compared to females (29-31).

In folk medicines, *Elaeagnus angustifolia* (Elaeagnaceae) is a Mediterranean medicine representative of the family Elaeagnaceae, commonly named oleaster, which is cultivated in north American, Eurasia as far southwards as Malaysia, Australia, northern regions of Asia to the Himalayas and Europe and for centuries in the desert and sub desert regions of western Asia including Iran (32-35).

A previous study showed that *E. angustifolia* flower and its derivatives had antibacterial and antifungal properties. It also led to cutaneous wound healing by increasing re-epithelialization and collagen deposition (31).

E. angustifolia flower is one of the herbal medications which, according to traditional medicine, is hot and dry, aromatic, and can stimulate sexual activity especially in young girls and women (36). It is also believed to have antioxidant effects (37). Due to its analgesic and anti-inflammatory effects, *E. angustifolia* extract is used in oils for external application (38). Moreover, one study showed *E. angustifolia* ointment to be effective in treatment of some skin disorders (39).

Other studies have also confirmed that the fruit core and leaves of this plant had analgesic and anti-inflammatory effects (40-43). Furthermore, one study evaluated the effect of aqueous and alcoholic extracts of *E. angustifolia* on intestinal smooth muscle relaxation in mice. It indicated that the presence of flavonoids in the fruit was effective in intestinal smooth muscle relaxation. Therefore, the researcher suggests that this plant is a suitable candidate for treatment of muscle-skeletal disorders (40) due to its muscle relaxant effect. On the other hand, *E. angustifolia* has been found to contain flavonoid components and some flavones, such as chrysin, (5, 7-dihydroxyflavone) which have a partial agonistic effect on benzodiazepine receptors. Central benzodiazepine receptor (BDZ-R) agonists have been known to induce multiple effects including anxiolytic, myorelaxant, anticovulsant, hypnotic and amnestic effects (44-46).

These two folk indications, anti-rheumatoid, anti-tetanus activities (40), anxiolytic, myorelaxant effects acting on central benzodiazepine receptors of flavonoid found in *E. angustifolia*, may make this plant a suitable candidate for inducing muscle relaxant activity for sexual dysfunction.

Up to now, several studies have been conducted on female sexual dysfunction in Iran. However, most of these studies have focused on the prevalence and types of sexual disorders and have paid

less attention to the treatment dimensions, including training, consultation and pharmacotherapy. Hence, the present study aimed to compare the effects of *E. angustifolia* flower extract and sildenafil citrate on female orgasmic disorder in the women referring to selected gynecology clinics affiliated to Shiraz University of Medical Sciences, Shiraz, Iran.

Methods

This study was a randomized clinical trial. Based on the study objectives and the previous studies conducted on the issue, considering error rate of 5%, power of 80%, minimum mean difference of 0.6, and variance of 0.92. A sample size of 126-subjects was selected for the study.

Overall, out of the 140 qualified women entered into the study, 125 ones (41 in the *E. angustifolia* group, 42 in the sildenafil citrate group, and 42 in the control group) completed the study. The study population included 18-40 year old women suffering from sexual dysfunction. The health centers were selected through stratified sampling and convenience sampling was used to select the women at each center. Then, the subjects were divided into *E. angustifolia* flower, sildenafil citrate, and control groups using stratified block randomization.

The inclusion criteria of the study were obtaining scores more than 22 in Female Sexual Function Index (FSFI), having normal menstruation, not being pregnant, not breastfeeding, without the history of heart attack, hypertension, and cardiovascular diseases, not consuming the medications which are effective in sexual function such as common antidepressants, not suffering from dyspareunia and vaginismus, not being menopausal, with 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. On the other hand, the exclusion criteria of the study were showing allergic reactions to medicines and not being able to continue consuming the drugs for any reason.

The data were collected through demographic information form, FSFI, and measurement of TSH and prolactin. FSFI which contains 19 items evaluates female sexual function in 6 domains of sexual desire, arousal, lubrication, orgasm, satisfaction and pain. The women were required to answer the questions according to their sexual desire and function during the past 4 weeks. In general, the scores ≤28 were 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.

The reliability of the whole questionnaire and the subscales was confirmed by Cronbach's alpha $\geq$0.70. Moreover, investigation of the validity of the Persian version of this questionnaire indicated a significant difference between the total mean score and the mean scores of the subscales in the two groups ($p\leq0.001$) (47-48). After obtaining written informed consents, TSH and prolactin were assessed in all the participants in order to reject 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 *gr* of *E. angustifolia* extract in two divided doses (2 capsules every 12 *hr*) for 35 days. The *E. angustifolia* capsule dosage was determined based on other studies conducted on the issue (49-50) and a pharmacognosy advisor. In the second group, the participants had to consume 50 *mg* sildenafil citrate tablets for 4 weeks. The dosage of sildenafil citrate was determined based on the previous studies most of which have used 50 and 100 *g* tablets (16, 51-53).

E. angustifolia capsules were made in the Pharmacology Department under the supervision of a professional counselor. Moreover, the placebo was prepared from starch in similar packages to *E. angustifolia* capsules.

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 participants were followed up twice a week through Short Message Sending (SMS) service and once a week through phone contact. After the intervention, the women completed FSFI.

Finally, the data were entered into the SPSS statistical software (version 18) and analyzed using paired t-test, one-way ANOVA, and Bonferroni post-hoc test. Besides, $p<0.05$ was considered statistically significant.

Ethical considerations: This research project was approved by the local Ethics Committee of Shiraz University of Medical Sciences and written in-

Table 1. Comparison of frequency of sexual dysfunction (orgasm disorders) before and after intervention between the intervention and control groups

Areas of sexual dysfunction (orgasm)	*E. angustifolia* flower capsule group	Sildenafil citrate group	Control group	Total	p-value
	Number (%)	Number (%)	Number (%)	Number (%)	
Before intervention	17 (41.5)	17 (40.5)	24 (57.1)	58 (46.4)	0.23
After intervention	12 (29.3)	7 (16.7)	21 (50)	40 (32)	0.004
p-value	0.267	0.006	0.549	--	

formed consents were obtained from all the participants. In addition, the control group was provided with the results after completion of the study.

Results

The mean age of the study women was 32.67± 5.05 years. Most of the subjects (67.2%) were between 30 and 40 years old. Besides, the age of marriage in 44% and 4% of the subjects were below 20 and above 30 years old, respectively. In addition, the mean length of marriage was 21.59± 4.61 years. Moreover, most of the participants (43.2%) had academic degrees and 33.6% had high school and diploma degrees. The results revealed no significant difference among the three groups regarding TSH (p=0.448) and prolactin levels (p=0.179) before the intervention. Also, no significant difference was found among the three groups concerning orgasmic disorder before the intervention (p=0.23). However, a significant difference was observed among E. angustifolia, sildenafil citrate, and control groups in this regard after the intervention (p=0.004) (Table 1).

According to the results of McNemar test, no significant difference was found in the control group before and after the intervention (57.1% vs. 50%; p>0.05). Also, no significant difference was observed in *E. angustifolia* group before and after the intervention (41.5% *vs*. 29.3%; p=0.267). On the other hand, a significant difference was found in the sildenafil citrate group before and after the intervention (40.5% *vs*. 29.3%; p=0.006) (Table1). Overall, *E. angustifolia*, sildenafil citrate, and control groups respectively showed 29.41%, 58.82%, and 12.5% reduction of sexual dysfunction score as compared to the condition before the intervention.

The findings of the current study indicated a significant difference between the EA group and the control group (p=0.001) and between the sildenafil citrate group and the control group (p<0.001) regarding the mean score of orgasm (Table 2).

The study results revealed no significant difference among the three groups concerning sexual satisfaction before the intervention (p=0.356). However, a significant difference was observed among the three groups in this regard after the intervention (p=0.03) (Table 3). According to the results of McNemar test, a significant difference was observed in *E. angustifolia* group before and after the intervention (p<0.001). On the other hand, no significant difference was found in the sildenafil citrate group before and after the intervention (p=0.06).

Overall, *E. angustifolia* and sildenafil citrate groups respectively showed 57.14% and 46.66%

Table 2. Comparison of average score of sexual function (in orgasm and sexual satisfaction area) before and after intervention between the tests and control groups

Areas of sexual function	*E. angustifolia*	Sildenafil citrate	Control	p-value
Orgasm				
Before intervention	3.31±1	3.48±0.94	3.18±1.19	0.418
After intervention	4.03±1.01	4.15±0.89	3.23±1.36	<0.001
p-value	<0.001	<0.001	0.715	--
Sexual satisfaction				
Before intervention	3.82±1.31	4.25±0.8	3.62±1.37	0.051
After intervention	4.75±1.2	4.73±0.78	3.74±1.65	<0.001
p-value	<0.001	<0.001	0.515	--

Table 3. Comparison of frequency of sexual dysfunction (sexual satisfaction area) before and after intervention between the intervention and control groups

Areas of sexual function (sexual satisfaction)	*E. angustifolia*	Sildenafil citrate	Control	Total	p-value
	Number (%)	Number (%)	Number (%)	Number (%)	
Before intervention	21 (51.2)	15 (35.7)	19 (45.2)	55 (44)	0.356
After intervention	9 (22)	8 (19)	18 (42.9)	35 (28)	0.03
p-value	<0.001	0.065	0.999	--	--

reduction sexual dysfunction score as compared to the condition before the intervention.

Also, a significant difference was observed between the EA group and the control group ($p<0.001$) and between the sildenafil citrate and control groups ($p<0.001$) regarding the mean score of sexual satisfaction (Table 2).

Discussion

In this study, EA, sildenafil citrate, and control groups respectively showed 29.41%, 58.82%, and 12.5% reduction sexual dysfunction score as compared to the condition before the intervention. This difference was statistically significant in the sildenafil citrate group ($p=0.006$), but not in *E. angustifolia* group ($p=0.267$). Nonetheless, a significant difference was observed between the two intervention groups and the control group regarding the mean score of orgasmic disorder ($p< 0.001$).

Caroso (2002) performed a study on 68 women between 19 and 38 years old who had no symptoms of sexual dysfunction in order to assess the effectiveness of sildenafil citrate. The participants had to consume sildenafil citrate and placebo for 4 weeks and were entered into the study based on Personal Experiences Questionnaire (PEQ). The study results showed that sildenafil citrate improved arousal ($p<0.01$), orgasm ($p<0.001$) and sexual satisfaction ($p<0.001$) compared to the placebo group (22).

Furthermore, Cavalcanti et al. (2008) carried out a research on 22 menopausal women who suffered from orgasmic disorder. The participants received either 50 *mg* sildenafil citrate (11 subjects) or placebo (11 subjects) in a single dose for 15 days. The results revealed a considerable increase in the vaginal blood flow in the sildenafil citrate group as compared to the placebo group ($p<0.05$) (18). These results were all in agreement with those of the present study.

In contrast, Dasgupta et al. (2004) investigated the effectiveness of sildenafil citrate in treatment of the women suffering from sexual dysfunction due to Multiple Sclerosis (MS). The study was conducted on 19 women with both sexual dysfunction and MS and the results showed that sildenafil citrate did not improve their sexual dysfunction ($p>0.441$) (54).

Similarly, Wylie et al. (55) reported that sildenafil citrate had no positive effects on women's sexual disability score, which is in contrast to the findings of the current study.

Sildenafil citrate is among the PDE5 inhibitors which by preventing cyclic guanosin monophosphate (CGMP) catabolism, leads to an increase in Nitric Oxide (NO) production, stimulation of NO release and increase in vaginal blood flow. This, in turn, results in an increase in sexual desire, orgasm, tissue hyperpolarization and relaxation, increase in blood flow, hyperemia and swelling (12), eventually leading to improvement of sexual dysfunction.

Up to now, no specific clinical scales have been used for diagnosis of female sexual dysfunction and no medications have been confirmed for its treatment. Yet, two strategies, *i.e.*, androgens and PDE5 inhibitors, are utilized for reduction of sexual disorders in women (56).

In the present study, *E. angustifolia* extract decreased the sexual dysfunction score as compared to the condition before the intervention and the control group; however, the differences were not statistically significant. To date, no studies have been conducted on the effectiveness of *E. angustifolia* flower in sexual disorders. Therefore, the study results were compared with those of the studies performed on other herbal medications used for sexual disorders.

Waynberg and Brewer (2000) aimed to find an alternative for chemical medications used for treatment of female sexual dysfunction and consequently, assessed Muira Puama and Ginkgo in 202 healthy women with low sexual desire. In that study, different aspects of the participants' sexual life were investigated before and one month after

the treatment. After consuming the supplements, the self-assessment questionnaire scores were higher than average in 65% of the participants. In addition, the results indicated a significant improvement in the frequency of sexual desires and fantasies, satisfaction with sexual life, intensity of sexual desires, ability to reach orgasm and intensity of orgasm ($p<0.001$) (57). Similarly, Ito (2006) reported that ArginMax (an herbal supplement) improved sexual dysfunction particularly regarding sexual desire (51% *vs*. 8% in the placebo group; $p=0.008$) (58).

E. angustifolia plant contains significant amount of flavonoids, terpenoids and sitosterol (59-62). Research has shown that certain flavonoids and sitosterol have analgesic and anti-inflammatory effects (62) and lead to vascular smooth muscle relaxation (63). Flavonoids are also believed to increase NO eventually resulting in vascular smooth muscle relaxation. Evidence has shown that NO, as an endogenous vascular dilator, plays a critical role in regulation of vascular tone (64-65) and is the main stimulant of cGMP production in smooth muscles (66). Increase in cGMP leads to an increase in the activity of kinase G protein which leads to vascular relaxation by phosphorylation of different molecules (67).

On the other hand, some experts believe that increase of cGMP results in smooth muscle vascular relaxation through other mechanisms (68). For instance, cGMP may lead to relaxation of smooth muscles by decreasing the intracellular calcium concentration (69). The positive effect of *E. angustifolia* on sexual dysfunction and sexual satisfaction in this study may be justified by the aforementioned mechanisms.

The findings of the present study indicated a significant difference between the two intervention groups and the control group concerning the mean score of sexual satisfaction ($p<0.001$).

Other studies have also found a significant relationship between improvement of sexual performance and sexual satisfaction (15, 57). Sexual relationships are among the main issues in marriage. Research has indicated that improvement of the quality of sexual relationships between husband and wife led to great satisfaction. It is, therefore, a decisive factor for marital and sexual satisfaction (2, 70-71).

Overall, it seems that identification and treatment of sexual dysfunctions can increase satisfaction and thus can improve the families' strength and survival and the community's health.

According to the previous studies, herbal medications, such as ArginMax, Ginseng, Ginkgo biloba, and ethanol extract (72-73) improved sexual dysfunction through an increase in NO production. NO is also among the compounds derived from *E. angustifolia* flower.

In conclusion, sexual dysfunction in women is a serious, complex, multi-factorial problem which might result from biological, psychological, cultural, social and hormonal factors. Since the participants had normal menstrual cycles, hormones, and endocrine parameters, their sexual dysfunction might have occurred due to other factors, including insufficient stimulation and lack of preparation. Phosphodiesterase-type 5 inhibitors (sildenafil citrate) and *E. angustifolia* flower also enhance vaginal smooth muscles relaxation, artery vasodilatation and swelling in the genital system, thereby improving sexual function. Other factors associated with sexual dysfunction include relational problems, lifestyle, and type of food regimen that were not investigated in the current study.

Conclusion

In this study, *E. angustifolia*, sildenafil citrate, and control groups respectively showed 29.41%, 58.82% and 12.5% reduction of changes as compared to the condition before the intervention. Thus, it seems that sildenafil citrate has been more effective in improvement of sexual dysfunction as compared to *E. angustifolia*. The findings of the current study can be used for improvement of women's and families' sexual health. Yet, further studies are recommended to be conducted using different doses of *E.angustifolia* at different times.

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Conflict of Interest

The authors declare no conflict of interest.

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