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Original article

Efficacy of *Saussurea costus* (Qost) Oil as an Iranian Traditional Medicine Product on Female Urinary Incontinence; Double Blinded Randomized Clinical Trial

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Abstract

Background and objectives: Urinary incontinence is a public complaint that causes discomfort, embarrassment and costs. Also, there are some limitations and insufficiencies of drug therapy and surgical complications. This study has compared the effect of *Saussurea costus* (qost) oil as an Iranian traditional medicine product and other contemporary medicine treatment methods on female urinary incontinence. **Methods:** A parallel double blinded placebo-controlled study was conducted. Thirty to 70 years old women with urinary incontinence were allocated in placebo and intervention groups, 41 patients in each group. Intervention and placebo groups received qost oil and placebo, respectively by local application twice daily below the navel without massage. The results were evaluated with valid questionnaires (ICIQ-SF and I-QOL). For evaluation, Chi-square test, independent-sample t-test and repeated measure analysis of variance were used. Significant p value was <0.05. **Results:** A significant decrease in mean scores of the questionnaires during the study was noted in the qost group compared to the placebo group (p<0.001). Before the intervention, thirty one patients in the placebo group and 33 patients in the qost group had mixed urinary incontinence (p=0.794). Urge symptom s(nocturia, urine frequency and urgency to urination) were completely discontinued in 25 patients in the qost group (78.1%) and 7 patients in the placebo group (22.6%) (p<0.001). **Conclusion:** The results suggested the oil to be effective in treatment of urinary inconsistence.

Keywords: Female urinary incontinence, Iranian Traditional Medicine, Persian Medicine, *Salas-albool*, *Saussurea costus*

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Introduction

Urinary incontinence (UI), is defined as involuntary urine leakage and is a very common complaint all over the world [1,2] which causes a lot of discomfort and embarrassment, as well as significant expenses to the individuals and the societies [3]. Female urinary incontinence includes three main subgroups: stress, urge and mixed. Stress urinary incontinence (SUI) is leakage of urine which occurs with rises in pressure of intra-abdomen such as laughing, sneezing, coughing or physical act. Loss of urine accompanied or followed by strong craving to

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void may be convoyed by nocturia and frequency known as urge urinary incontinence (UUI) and mixture of urge and stress symptoms called mixed urinary incontinence (MUI) [2,4]. In Europe and Canada, the incidence of urinary incontinence in young women is reported to be 18% and is twice likely to occur in women than in men [5]. Not so long ago in the United States of America (USA), the cost of UI alone was 16.3 billion dollars of which three-quarter of the cost has been spent on the management of the affected women [1]. UI has a negative impact on the normal activities of life, the feeling of mental relaxation and the quality of life in patients such as avoiding the presence of the community and reducing social relationships and physical activity [5]. The usual approaches to the treatment of UI include conservative managements such as pelvic floor muscle exercises, functional electrical stimulation, behavioral therapy and intra vaginal devices. Other approaches are pharmacologic interventions such as beta-adrenergic agents and anticholinergic drugs, and finally surgery if there is no response to initial treatments [4-6]. Conversely, there is still no well-defined general and universal therapeutic success for women with SUI [7]. Surgery has early and late complications [8] and sometimes it needs to be repeated [5]. Overall, there is no mentioned effectiveness of drugs, and there are also significant risks for some of them [6]. Thus, the ineffectiveness of drug treatments and significant complications of UUI is evident [9] and it seems necessary to find effective, low-risk and low-cost drugs in order to control this disease. In this study, our purpose was to evaluate the effect of qost oil, topical product of Iranian Traditional Medicine (ITM) on female UI.

Material and Methods

Ethical considerations

The study plan was according to the recommendations of Announcement of Helsinki (2013 revision). Also, the study procedure was revised, accepted and observed by the local Ethics Committee of Tehran University of Medical Sciences (registration number: IR.TUMS.REC.1394.1113), and documented in Iranian Registry of Clinical Trials (registration ID: IRCT2015110924970N1). All patients signed informed consent before enrollment.

Plant material

Dried roots of *Saussurea costus* (Falc.) Lipsch (qost) were purchased from local herbal market in Tehran. The plant sample was identified by Dr. Gh. Amin (botanist) and a voucher specimen was kept at the Herbarium of Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran (PMP-240).

Preparation of qost oil and placebo

Hydro alcoholic extract was made from 100 g of plant's root powder in 600 mL 25% ethanol for 24 h with continuous shaking. The extract was then mixed with 800 g cold pressed sesame oil and the mixture was boiled until all water was evaporated [10]. The placebo group received cold pressed sesame oil.

Study design

The study was a double blinded randomized clinical trial (RCT) in which randomized blocking method was done by the consultant's statistics.

Eligible patients

Women with SUI or MUI randomized (1:1) into placebo and qost groups were enrolled in the study. Each group for analysis consisted of 41 subjects who were referred to pelvic floor clinic in Imam Khomeini Hospital of Tehran University of Medical Sciences, Tehran and ITM center in Ardabil, Ardabil.

Inclusion criteria

Thirty to 70 years old women with SUI or MUI; being symptomatic for at least 3 months; drug wash out period 2 weeks; who were willing to participate in the research and had signed a consent form after explaining the research objectives of the research were enrolled in the study.

Exclusion criteria

Women with acute or recurrent urinary tract infection; pregnancy or lack of contraception; allergy to oily drug products; chronic degenerative neuromuscular disease; presence or previous bladder cancer; pain of the bladder or painful urine voiding; disease or consuming drugs that were effective on urinary system function such as diuretics; and record of pelvic surgery during the past one year were excluded.

Intervention

Fifteen drops (2.3 mL) of oils in both groups were used by local application twice a day to the

area between the navel and pubic region without massage (to examine purely the effect of oils).

Outcome measurements

The effect of *Saussurea costus* oil, an ITM product was evaluated on the severity and quality of life of female SUI and MUI. This survey was designed according to International Consultation on Incontinence Questionnaire- urinary incontinence Short Form (ICIQ-SF) and Incontinence Quality of Life questionnaires (I-QOL) that were validated in Persian [11,12] compared to the placebo. The ICIQ-SF questionnaire measures the severity of UI and its effect on the quality of life of the patients. This questionnaire is also suitable for screening of UI and determining the type of urinary incontinence [13] which has been translated into multiple languages [11]. It is a 6-item questionnaire. The full ICIQ-SF score is obtained by adding the 3 individual domain scores including the frequency of urinary incontinence, the volume of leakage and the consequence of the disease on quality of life. Reduction in the scores shows improvement in the condition of the disease. In this study, a significant difference of 8 points was acceptable. The reliability of the volume and frequency of incontinence urinary leakage in this mental questionnaire has been proven with objective tests and other para clinical tests. Also, the reliability of patient's response to this questionnaire is shown after treatment [14]. The Persian version of the I-QOL can be a profit for assessing QOL of women UI in Iran. The questionnaire has 22 questions with 5 options for each question for assessing the quality of life which will be lowered as the situation improves [12].

Side effect controlling

Drug Complaint Questionnaire was prepared based on Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0. Evaluation of possible side effects was done on weeks three and six of the study and patient's reports were recorded. In addition to preventing possible skin complications for all specimens, the first dose of 3 to 5 drops of oil was used for testing by rubbing on the arm and in the absence of local symptoms for 12 h, the drug was used on the original site.

Statistical analysis

Chi-square test, independent-sample t-test, and repeated measure variance analysis were used for statistical analysis of this study. Because p-value was less than 0.001 in the calculations, the adjust test was not necessary. Significance p-value was <0.05.

Results and Discussion

At the end of the study, three out of 44 women in the qost group and four out of 45 women in the placebo group dropped out of the study. The total of the study participants involved were 82 women (41 in the intervention group and 41 in the control group). The demographics and baseline measurements for the participants have been shown in figure 1 (CONSORT flowchart). Baseline characteristics were well balanced in terms of age, BMI, parity, constipation, type of incontinence, urinary frequency, nocturia, scores of QOL questionnaire and the characteristics of UI upon ICIQ-SF questionnaire ($p>0.20$ in all the terms) (table 1).

At weeks three and six (end of intervention), and 4 weeks after the end of intervention, a significant reduction in mean full scores of ICIQ-SF questionnaire ($p<0.001$) was noted in the qost group compared to the placebo group. There were significant reduction of the 3 individual domain scores of ICIQ-SF questionnaire (questions 3, 4 and 5), in the qost group compared to the placebo group. (table 2 and figure 2).

Comparing the percentage reduction in full scores mean of ICIQ-SF questionnaire in weeks three and six and four weeks after the end of intervention showed that the qost group confirmed a mean of (65.307, 86.607 and 87.60%) reduction versus (22.396, 35.86 and 34.860%) in the placebo group, respectively. Also, a significant reduction in mean scores of I-QOL questionnaire was detected at weeks three and six and four weeks after the end of intervention in the qost group compared to the placebo group ($p<0.001$) (table 2 and figure 3). The percentage reduction in the scores of I-QOL questionnaire at the same times, demonstrated that the qost group confirmed a mean of (57, 85 and 85.6%) reduction versus (20, 46 and 43%) in the placebo group. Among the 41 patients who entered statistical calculations in each group, 31 in the placebo group and 32 patients in the qost group had MUI ($P=0.794$).

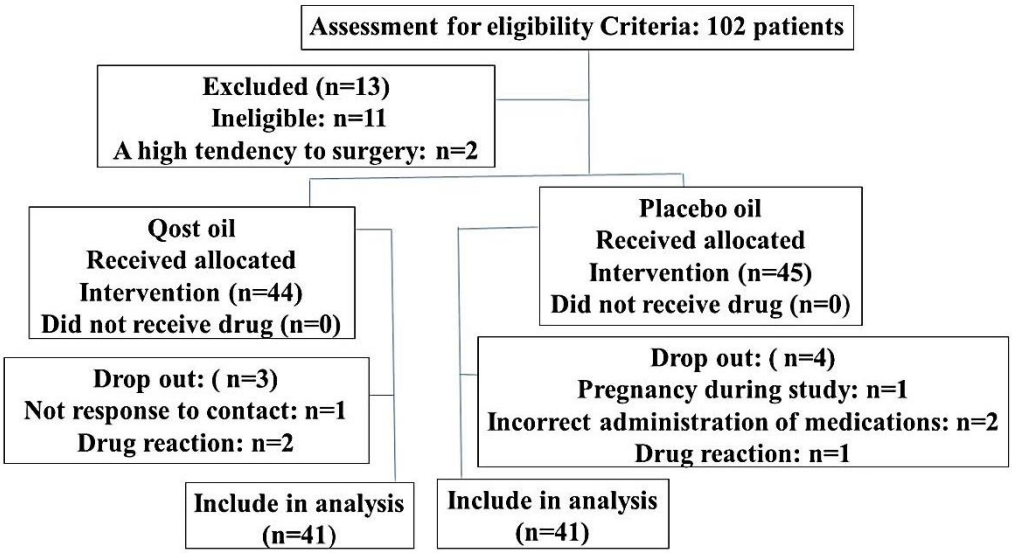

Figure 1. Consort flowchart of the inclusion, allocation and outcomes of the trial

Table 1. Characteristics of subjects at baseline

Variables	placebo group n=41 Mean (SD)	Qost group n=41 Mean (SD)	p value
Age (years)	52.98 (9.224)	52.39(9.821)	0.782
BMI (kg/m^2)	32.2895 (5.02170)	30.9415(5.06688)	0.230
Nnumber of deliveries	4.51 (2.590)	4.00 (2.499)	0.360
Nnumber of pregnancies	4.59 (2.588)	4.00 (2.439)	0.295
Constipation (%)	28(68.3)	30(73.2)	0.627
Urine frequency (%)	28(68.3)	28 (68.3)	1.00
Nocturia (%)	20(48.8)	21(51.2)	0.825
Kind of incontinences (SUI) (%)	10(24.4)	9(22)	0.794
Kind of incontinences (MUI) (%)	31(75.6)	32(78)	0.794
TS–ICIQ–SF (score)	12.10 (5.276)	12.02 (5.265)	0.950
TS-I-QOL (score)	42.63 (23.935)	)22.632(39.56	3.073
ICIQ-SF -3 (score)	2.283 (1.263)	2.66 (1.237)	0.538
ICIQ-SF -4 (score)	3.20 (2.016)	3.20 (2.159)	1.00
ICIQ-SF -5 (score)	6.20 (3.068)	6.39 (2.940)	0.769

SD: standard deviation; BM: body mass index; TS-ICIQ-SF: total score of ICIQ-SF questionnaire at first visit; TS-I-QOL: total score of I-QOL questionnaire at first visit; ICIQ-SF -3: the frequency of urine leakage according to question 3 of the ICIQ-SF questionnaire in the first visit; ICIQ-SF -4: volume of incontinence urine leakage according to question 4 of ICIQ-SF questionnaire in first visit; ICIQ-SF -5: quality of life according to question 5 of ICIQ-SF questionnaire in the first visit

At the end of the study, the urge symptoms were completely discontinued based on the questionnaire in 25 patients in the qost group (78.1%) and 7 patients in the placebo group (22.6%), ($p<0.001$), (table 2).

There was no report of beta-adrenergic agents and anticholinergic drugs side effects that were used for UUI treatment and alpha adrenergic agonists side effects that were used for treatment of SUI. These side effects have been listed in the discussion section of this article.

In one patient in qost group, we observed redness, itching and burning in the arm during drug test and in another patient pain sensation was created in the abdomen during oil application. Pain sensation was created in one patient of the placebo group, too. Abdominal pain improved in both patients by drug discontinuation.

In table 2, the complete comparison of mean, standard deviation and p-value for study variables were presented in two groups at 0, 3 and 6 weeks from the start of the intervention,

and 10 weeks later (4 weeks after the end of intervention).

To the best of our knowledge, this is the first RCT to evaluate the efficiency of one topical production on the severity and quality of life of female UI. Our hypothesis was that qost oil could improve the severity and quality of life of female UI. The herb called qost (*Saussurea costus*) and its oil is one of the recommended treatments for UI which is effective in eliminating "cold" and "wet" temperament that affect the bladder wall, and relax the bladder sphincter muscle, which leads to their dysfunction [15-17]. Avicenna (980- 1037 AD) believed that the root of qost would be beneficent to all tissues and organs which needs to be warmed up and it can absorb and eliminate waste materials of cellular metabolism from depth of tissues and organs. It can also be effective in organs with impaired function due to tissue loosening [15].

Qost oil can strengthen the organs and destroy the material deposited in the tissue without the production of any additional waste [17]. Following the ITM view, our aim for treating urinary incontinence were warming, strengthening and removing excessive bladder moisture; while in previous animal studies, the effects of qost extracts on the immune system, cardio tonic effects and beneficial effects of qost oil on infections caused by *Staphylococcus aureus* have been shown to be satisfactory [18-21].

According to our study, the effect of topical application of qost oil on reducing the symptoms and improving the quality of life of SUI and MUI, was created in short-term and remained stable four weeks after treatment discontinuation ($p<0.001$). Improvement of the SUI and MUI symptoms in the qost group was more than the placebo group, also showed this oil could be effective in improving the symptoms and quality of life of all three types of female UI. However, for more precise judgment, supplementary studies with higher sample sizes and longer study times seem to be necessary.

The usual attitude for UI treatment is beginning with noninvasive behavior alterations, followed by devices and pharmacologic mediations. Surgery is the last approach in patients who do not respond to other treatments [22]. The following is the overview of treating methods of three important types of female UI compared with the results of this study. The results of this trial showed complete improvement in a 6 weeks period and non-relapse of symptoms, at least one month later, for more than 87% of patients with SUI and MUI. However, this method is simple and non-invasive compared to many conservative therapies such as posterior tibial nerve stimulation, extraterritorial corneal extrusion magnetism, mechanical devices such as pessaries and urethral plugs [23].

Table 2. Comparison of mean, standard deviation and p value for study variables in two groups at 0, 3 and 6 weeks after start of the intervention, and 10 weeks later (4 weeks after the end of the intervention)

	Baseline			**Week 3**			**Weeks 6**			**Week 10 (4 weeks after the end of intervention)**		
Follow-up measures (changes from baseline)	Qost N=41	Placebo N=41	P value	Qost	Placebo	P value	Qost	Placebo	P value	Qost N=41	Placebo N=41	P value
MS-ICIQ-SF Mean(SD)	12.02 (5.265)	12.10 (5.276)	0.950	4.17 (4.248)	9.39 (5.865)	0.000	1.73 (3.362)	7.76 (5.999)	0.000	1.49 (3.828)	7.88 (6.660)	0.000
MS-I-QOl Mean(SD)	39.56 (22.632)	42.63 (23.935)	0.552	16.98 (15.204)	33.8 (21.346)	0.000	5.85 (10.558)	23 (18.412)	0.000	5.66 (12.078)	24.29 (22.704)	0.000
MS-ICIQ-SF-3 Mean(SD)	2.66 (1.237)	2.83 (1.263)	0.538	0.78 (0.962)	2.15 (1.424)	0.000	0.39 (0.802)	1.78 (1.351)	0.000	0.39 (0.972)	2.54 (5.532)	0.017
MS-ICIQ-SF-4 Mean(SD)	3.2 (2.159)	3.2 (2.016)	1.000	1.02 (1.491)	2.61 (2.096)	0.000	0.44 (1.141)	2.29 (2.250)	0.000	0.51 (1.502)	2.39 (2-365)	0.000
MS-ICIQ-SF-5 Mean(SD)	6.39 (2.940)	6.2 (3.068)	0.769	2.34 (2.446)	4.61 (2.965)	0.000	0.9 (1.882)	3.71 (3.124)	0.000	0.82 (2.123)	3.65 (3.446)	0.000
US improvement Number (%)	32	31	0.794	5 (15.6)	2 (6.5)	0.247	21 (65.6)	4 (12.9)	0.000	25 (78.1)	7 (22.6)	0.000

SD: standard deviation; MS-ICIQ-SF: mean score of ICIQ-SF questionnaire; MS-I-QOl: mean score of I-QOL questionnaire; MS-ICIQ-SF-3: mean score of incontinence urine leakage frequency according to question 3 of the ICIQ-SF questionnaire; MS-ICIQ-SF-4: mean score of incontinence urine leakage volume according to question 4 of ICIQ-SF questionnaire; MS-ICIQ-SF-5: mean score of Quality of life according to question 5 of ICIQ-SF questionnaire; US: urge symptoms.

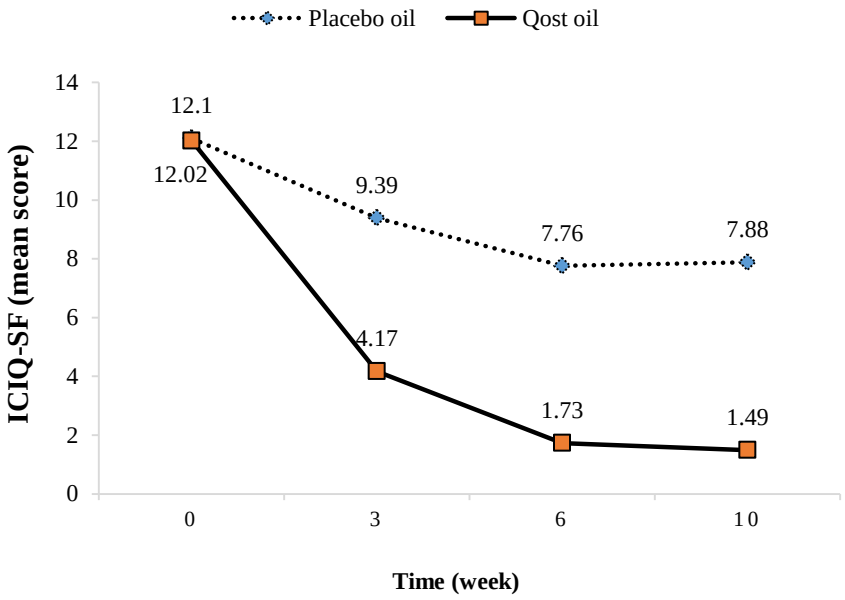

Figure 2. Mean scores of ICIQ-SF questionnaire at different times in two groups

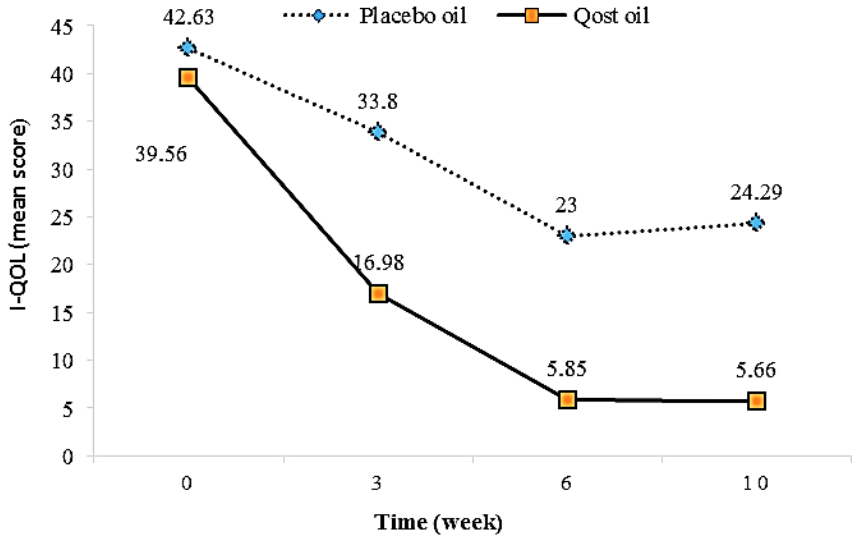

Figure 3. Mean scores of I-QOL questionnaire at different times in two groups

Compared to qost oil which can provide significant therapeutic effects for all three types of urinary incontinence in 6 weeks, the main support of behavioral therapy (pelvic floor muscle exercises) uses only for SUI treatment. This method at least needs a period of three months treatment,and only about 38% of patients with pure SUI aptitude would be cured [22]. Meanwhile, methods such as pelvic floor exercise, weight loss, reduced cigarette smoking, reduced fluid intake and relief of constipation can be in line with our proposed treatment and help the treatment. Food and Drug Administration (FDA) did not approve any medications such as duloxetine (cymbalta) and alpha-adrenergic agonists for example pseudoephedrine and phenylephrine for the treatment of SUI. In theory, alpha-adrenergic agonists (e.g. phenylephrine and pseudoephedrine) reduce SUI with urethral constriction [24] but there is only weak confirmation to provide their dominance over the placebo [24,25]. Insomnia, anxiety, hypertension, arrhythmias and stroke are the adverse effects [25]. Most women withdrew from treatment within four weeks, mentioning side effects (45%) or absence of efficiency (24%) [22]. For

treatment of MUI and UUI cure is not often attained just with medication therapy, though in several trainings, development over placebo is unassertive. Variety of medication and behavioral managements are more operational than any method alone [1,26]. But in this study, reliable therapeutic effects have been observed for urinary incontinence with a topical medication, without considerable side effects.

Anticholinergic drugs that are used for treatment of MUI and UUI have adverse effects including palpitations, tachycardia, edema, psychomotor retardation, confusion, nausea, vomiting, constipation, abdominal pain, urinary retention, dry mouth and blurry vision [22]. Due to adverse effects, the American Geriatrics Society mentions avoidance of these treatments in older adults except when no replacements are accessible [27]. Other contraindications of anticholinergics are gastrointestinal obstruction/gastric retention, narrow-angle glaucoma and dementia [24]. In spite of the fact that β-adrenergic agonists are accepted by the FDA in 2012, but mirabegron (myrbetriq) (a new class of drugs used in UI treatment) has corporate adverse effects such as constipation, diarrhea, nausea, headache and dizziness; also, it increases blood pressure [22]. No symptoms were observed in any of the patients with the same side effects of the mentioned drugs in the present study. Conversely, further studies are needed to confirm the absence of these complications in qost oil. Also in some studies of UUI, mirabegron resulted in only one to two fewer incontinence occurrences per day, similar to sustained-release tolterodine (detrol) [28]; but according to the results of our clinical trial, the therapeutic effect of qost oil is more. Estrogen is occasionally used to treat UUI, but FDA has not accepted intravaginal and systemic estrogens. Systemic estrogen has been reported to develop worsen incontinence [29,30]. Surgical methods are successful in treatment of SUI, but they are invasive and expensive and have surgical complications [22]. Surgical treatments for controlling UI such as sacral nerve stimulators can develop symptoms in only up to two third of patient's involved, which is distinguished since these procedures are used solitary for symptoms that are intractable to other managements. Implantable devices are expensive with surgical complications [22]. It seems that the treatment used in the present study was less invasive and more effective (87.60 %) than the surgical methods and did not have the same complications as surgery. Though, a higher sample size is required for a more exact examination of the possible complications and shelf life treatment (prolonged survival).

The search of local therapies for UI had limited results. Except for vaginal estrogen used in urge incontinence which was not approved by the FDA [22], oxybutynin is the only drug that is used as a topical gel and transdermal patch for controlling UUI. This patch has suitable effects in reducing daily episodes of involuntary, frequent urination and improving quality of life. Although transdermal delivery of oxybutynin decreases the risk of dry mouth (prevalence 7.0%) and other oral administration anticholinergic side effects, local skin reactions have been common (31.8%) and caused drug interruption in patients. Also, high expenses of the transdermal form of drug, has created a potential barrier to long-term agreement with the treatment (6 months) [31]. Qost oil seems to be the first topical herbal product applied to treat urinary incontinence and has been able to respond in a shorter time than the oxybutynin transdermal patch as a lasting cure for all types of women UI. For the definitive confirmation of these results, studies designed with higher sample sizes are required.

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Author contributions

Zahra Niktabe did the experimental parts; Tahereh Eftekhar and Malihe Tabbarrai supervised the clinical parts of the project; Mehran Mirabzadeh Ardakani supervised preparation of the drug; Mir Saeed Yekaninejad was the statistics consultant; Laila Shirbeig was Persian Medicine advisor and scholarly content editor; Nastaran Ebadi and Sahar Bagheri helped in preparation of the drug; Nematollah Masoudi was statistics consultant, scholarly content editor and final text editor.

Declaration of interest

The authors declare that there is no conflict of interest. The authors alone are responsible for the content of the paper.

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Abbreviations

UI: urinary incontinence; ITM: Iranian traditional medicine; SUI: stress urinary incontinence; MUI: mixed urinary incontinence, UUI: urinary incontinence; FDA: Food and Drug Administration; RCT: randomized clinical trial; ICIQ-SF: International Consultation on Incontinence Questionnaire-urinary incontinence Short Form; I-QOL: Incontinence Quality of Life; CTCAE: Common Terminology Criteria for Adverse Events; TVT: tension-free vaginal tape