Complementary Therapies in Clinical Practice 20 (2014) 230–236

Contents lists available at ScienceDirect

Complementary Therapies in Clinical Practice

journal homepage: www.elsevier.com/locate/ctcp

Efficacy of *Boswellia serrata* L. and *Cyperus scariosus* L. plus pelvic floor muscle training in stress incontinence in women of reproductive age

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Keywords:
Stress urinary incontinence
Unani medicine
Boswellia serrata
Cyperus scariosus
Pelvic floor muscle training

A B S T R A C T

Introduction: To determine the efficacy of combining of *Boswellia serrata* L. resin and the root of *Cyperus scariosus* L. plus PFMT in reproductive age women with stress urinary incontinence.
Methods: A prospective, single-blind, placebo-controlled, randomized trial was conducted. The patients were randomized to receive orally either combination of equal quantity of *B. serrata* and *C. scariosus* (2g) ($n = 30$) or placebo ($n = 30$) respectively twice daily for 8 weeks in addition to pelvic floor muscle training in both groups. The outcome was one hour pad test. The results were analyzed using parametric and nonparametric test.
Results: The improvement in the test and control group was 60% and 37% respectively. Between the group comparison was statistically significant ($P = 0.035$). The intra group comparison of one hour pad test was statistically significant in both groups ($P < 0.001$). No adverse effects were noted.
Conclusion: The test group was more effective than control group in women with SUI.

1. Introduction

Urinary incontinence (UI) is an under-reported, undiagnosed, and often untreated medical condition that significantly impacts on quality of life for women of all ages [1,2]. Of the six major types of UI, stress urinary incontinence (SUI) is the most common, reported by approximately 50% of incontinent women [3]. It is frequently reported by women of childbearing age [4].

Stress urinary incontinence (SUI) is a major health problem with significant personal, family and economic costs that has substantial and important effects on health-related quality of life [5]. Other adverse effects of SUI include social isolation, loneliness and sadness, psychiatric illness including depression and embarrassment which affects activities of daily living, stigmatises, affects sexual relationships and disturbs sleep [4,5]. SUI is defined as the involuntary loss of urine that occurs with physical exertion and rise in abdominal pressure (coughing, sneezing, straining, jumping, and running) [3,6]. The prevalence of urinary incontinence is expected to increase as a result of demographic change and the increasing elderly population [5]. Pathophysiologically, SUI can be the result of bladder neck/urethral hypermobility and/or neuromuscular defects (intrinsic sphincter deficiency) [3,6]. Internal sphincter deficiency (ISD) can be defined as damage to the urethral sphincteric mechanism, regardless of etiology. The urethra might be damaged owing to fixation (as in cases of spina bifida), prior surgery, denervation or muscle damage during childbirth. Internal sphincter deficiency and hyper mobility can exist concomitantly as well as alone [7]. Despite its high prevalence, its association with adverse health outcomes and the fact that there are evidence-based treatment options available, many health-care practitioners do not routinely screen for SUI [8]. There are broad varieties of therapies for the treatment of stress urinary incontinence (SUI) in adult women, ranging from physiotherapy to surgical interventions [9]. Therapies include medical management, Kegel exercises, biofeedback, and electrical stimulation. All of these treatments are established methods used in urinary incontinence [5]. The pharmacological treatment of SUI includes α-adrenoceptor (α-AR) agonists, β-AR agonists, estrogens and tricyclic antidepressants (TCAs) have been used off-label. However, the effectiveness of these drugs from randomized controlled trials (RCTs) shows little or no evidence and several of them may cause significant adverse effects. Imipramine, a TCA, is used occasionally to treat SUI. This drug inhibits the re-uptake of

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http://dx.doi.org/10.1016/j.ctcp.2014.08.003
1744-3881/

noradrenaline and serotonin in adrenergic nerve endings, which might increase the contractile effects of noradrenaline on urethral smooth muscle. No good-quality RCTs have investigated the efficacy of imipramine. Adverse effect of TCAs includes orthostatic hypotension, dry mouth, constipation, retention, and falls. Serotonergic agonists generally suppress parasympathetic activity and enhance sympathetic and somatic activity in the lower urinary tract, which, together, promote urine storage [3]. In a systematic literature review, the Cochrane Incontinence Group concluded that pelvic floor muscle training should be offered as first-line conservative management to women [10]. A subsequent Cochrane review also concluded that PFMT is effective for women with SUI and is superior to no treatment [11].

In the Unani system of medicine oleo-gum-resin of *Boswellia serrata* (*kundur*) and root of *Cyperus scariosus* (*nagarmotha*) have been used traditionally to treat urinary incontinence. These plant products have astringent property and tone the muscles [12]. These herbs are also known for their effects on the nerves, astringent antidepressive, sedative and analgesic properties. In animal studies no toxicity has been reported for both herbs in therapeutic doses [13,14].

Although these herbs are mentioned in classical texts and are frequently used, however, documentations are not available. Combination of these two Unani herbs was selected to validate their efficacy in reproductive age women with SUI. The research question was whether the use of *B. serrata* and *C. scariosus* plus PFMT was effective in ameliorating SUI in women of reproductive age. The aim of this study was whether the combination of *B. serrata* and *C. scariosus* plus PFMT compared with placebo plus PFMT would be effective in improving SUI.

2. Material and methods

2.1. Study design

A prospective, parallel, single centre, single-blind, simple randomized, placebo-controlled study was conducted at the outpatient department of the National Institute of Unani Medicine (NIUM), Bangalore, India between March 2012 and February 2013. The Institutional Ethical Committee of NIUM (Memo No.: NIUM/IEC/2010-11/23/ANQ/05) approved the protocol and all the patients gave written informed consent. The study was performed in accordance with the Declaration of Helsinki and GCP guidelines issued by the AYUSH Dept, Ministry of Health, Government of India. The trial is registered in clinical trial registry-India (ICMR) with ref no. REF/2014/01/006298. A total of 60 patients presenting with stress urinary incontinence for at least six months who fulfilled the inclusion criteria were recruited.

2.2. Participants

2.2.1. Inclusion and exclusion criteria

Parous and menstruating women aged 18–55 years having symptom of predominant SUI with or without grade 1, 2 and 3 genital prolapse, an average daytime voiding interval >2 h, a nocturnal voiding frequency ≤2 per day and a positive cough stress test (supine full bladder) observed on physical examination at visit 1 were included. Hematological and biochemical parameters within normal range and willing to sign the informed consent were included. Patients were excluded if they were on pharmacological treatment for symptoms of urinary incontinence in preceding one month and continence surgery within 6 months, enuresis, continuous leakage of urine, pelvic pathology (fibroid, malignancy, fistula), systemic and endocrine diseases (asthma, tuberculosis, diabetes mellitus, uncontrolled hypertension or any psychiatric disorders), pregnant women or nursing mothers, obstruction of urethra, cognitive and psychiatric impairment and drug treatment for depression [15].

2.3. Study procedure

During the selection procedure, all patients underwent assessment including urogynecological history, physical examination, a cough stress test, a 1-h pad test, and investigations. Clinical variables were also collected; how long they had the complaint of stress urinary incontinence, incontinence frequency episodes [Never (0); About once a week or less often (1); Two or three times a week (2); About once a day (3); Several times a day (4) and All the time (5)], amount of leakage (whether you wear protection or not)? [None (0); A small amount (2); A moderate amount (4) and A large amount (6)], pad usage (yes or no) and number of pads (1-2, 3-4, or >4 units/day) [16], leakage on sitting to standing, difficulty in emptying the bladder, and pain or discomfort in the lower abdomen or genital area or pain in the middle of abdomen as bladder fills.

To evaluate mental status, simple observation of the patient's orientation, speech, memory, level of consciousness and comprehension was performed. In complete pelvic examination, stress test, pelvic floor muscular strength (PFMS), genital prolapse, per speculum and per vaginal examination was performed. For stress test, patient was asked to perform a valsalva maneuver or cough repetitively and leakage from the urethra was observed. PFMS was noted by vaginal palpation [17]. Genital prolapse was graded using the Baden–Walker classification system [18]. Routine investigations like complete blood picture, erythrocyte sedimentation rate (ESR), random blood sugar and routine urine examination were done to exclude general diseases. Baseline (visit 1) and post treatment (visit 5), complete blood picture, ESR, random blood sugar, alkaline phosphatase SGOT, SGPT, serum creatinine and blood urea were done to assess the safety of test drugs. The specific investigations such as thyroid profile, urine culture and pelvis ultra sonography test were done to exclude, thyroid dysfunction, urinary tract infection and uterine fibroid, and malignancy respectively.

2.4. Assessment tools

All patients underwent standardized 1-hr pad test as per the International Continence Society to assess incontinence in the present study [19].

2.4.1. Standardized one hour pad test

In the present study, pre and post pad weight at baseline (visit 1) and post treatment (visit 5) was determined using digital electronic precision balance scale with accuracy $d = 0.01$ g and capacity 600 g (model: FR-H). Pad weight increase of1g/h or greater was considered abnormal [19]. The pad test is used for an objective quantification of urinary incontinence. Versi et al. found a positive predictive value of 92% and a negative predictive value of 53% of it when screening for lower urinary tract dysfunction [20]. Lose and Versi used the same test for diagnosing genuine stress incontinence in patients who had no other urodynamic abnormality, the positive and negative predictive values were 91% and 72% respectively [21].

2.5. Follow up and assessment

Follow-up visits were scheduled every fortnightly during treatment of 8 weeks and one follow up after a month without treatment. The patients were asked about improvement or worsening of their symptoms at each visit and 1-hr pad test was

performed at visit 1 and visit 5. Adverse drug reactions were noted during the treatment protocol.

2.6. Withdrawal criteria

Patients were withdrawn who failed to follow the protocol or in which drug adverse reactions were observed.

2.7. Intervention

In the test and control group, combination of trial drugs plus PFMT and placebo plus PFMT was given respectively.

2.7.1. Selection and preparation of trial drugs

The combination and dosage of trial drugs, oleoresin of *B. serrata* and root of *C. scariosus* has been selected from the Unani pharmacopeia [12].These herbs were supplied by the pharmacy of the National Institute of Unani Medicine, Bangalore. Botanical identification of the desired quality was in accordance with the guidelines of pharmacopoeial standard of Unani formulation. Both plant materials were identified and confirmed by the pharmacognosist of the institute and specimens [voucher no: 09/UQ/Res/2013] were submitted to the pharmacy Department for further reference.For the preparation of the dosage form both the plant materials after identification, was cleaned and separately powdered in hammer mill. Powdered drug was sieved through mesh no. 100. Both powder were taken in equal quantity by weight and mixed in mixer. Blended powder was filled in 00 size capsules with manual capsule filling machine. Each capsule was containing 1 g powder.

The placebo (microcrystalline edible cellulose) and test drugs powder was put in capsules. Fortnightly, 60 capsules were supplied in an individual pack for each patient and compliance was checked after each course of treatment. In the test and control group, patients were advised to take two capsules (1 g of powder in each capsule) orally, twice daily for eight weeks.

2.7.2. Method of pelvic floor muscle training (PFMT)

In the present study, patients in both groups were instructed how to carry out specific pelvic-floor exercises. A physiotherapist provided a 30-min training session at visit 1, and at each subsequent visit with the researcher. Patients were advised to perform a set of progressive specific exercises along with Kegel's exercise daily at home for 12 weeks. Initially, patients were assigned exercises that provided a general awareness of their pelvic-floor musculature. This exercise regimen was adopted from Deborah and co-workers study [22]. The first awareness exercise consisted of stopping and starting the flow of urine. Second, an overflow exercise was given that consisted of squeezing the thighs and buttocks together and tightening the abdominal muscles. The purpose of the overflow exercise was to achieve an overflow of muscle contraction into the pelvic-floor muscles. Thirdly, participants were asked to perform posterior pelvic tilts to increase the strength of their lower abdominal muscles, which are important in supporting the pelvic viscera [22]. Patients were next instructed to perform a pure pelvic-floor contraction (Kegel's exercises), gradually increasing the frequency and duration of the contraction. This exercise consisted of a voluntary inward and upward contraction or squeeze of the pelvic floor. Twenty contractions four times a day, to as many as 200 contractions per day, were advised. The recommended posture to be adopted during the prescribed exercise regimen varied and included sitting, kneeling, standing, lying down and standing with legs astride [23].

2.8. Outcome

The therapeutic outcome measure was changes in one hour pad test. The result was divided into two groups: Improved (urine loss $\leq$1 g) and not improved (urine loss $\geq$ 1 g).

2.9. Sample size estimation

Based on proportion value of cure rate of 78.6% and 59.6% obtained from an earlier study [24], a total sample size of 55 participants ($n1 = 27$, $n2 = 28$) would be required to have a 90% power with an alpha = 0.05 to detect improvement of 50% in SUI considered to be clinically meaningful. Hence, in the present study a total sample size of 60 patients was taken allowing for a 10% dropout rate.

2.10. Randomization and blinding

After the screening procedure, patients were randomly allocated in a 1:1 ratio to test or placebo group. The random allocation sequence was in single blocks, using a single sequence of random assignment, obtained using a computer generated randomization list (http://www.graphpad.com/quickcalcs/randomize2/). An open list of random numbers was used and the sequence was concealed from the researcher (data collector) until the interventions were assigned. The patients were blinded to the intervention and sample matching was done by masking the identity of drugs (the powder of herbs and placebo [cellulose] was put in the capsules and dispensed).

2.11. Data analysis

2.11.1. Statistical software

The Statistical software Graph Pad Instatversion 3.00 for window (Graph Pad Software, San Diego, Calif, USA), and the contingency table of more than 2x2, online website (http://www.physics.csbsju.edu/cgi-bin/stats/exact) was used for the analysis of the data. Microsoft word and Excel have been used to generate graphs and tables.

2.11.2. Statistical analysis

Descriptive analysis was performed to give the means of the frequencies of the categorical variables and measurements of the position and dispersion of the continuous variables. Results for continuous measurements were presented as mean ± SD and results on categorical measurements were presented as number (%). For all statistical tests, *P* values were used and the alpha was set to 0.05. In comparisons of continuous variables between pairs of independent and dependent groups, the unpaired and paired Student *t* tests respectively were utilized. All outcomes were analyzed according to the intention-to-treat principle using data from all randomized subjects with at least one post-randomization outcome measure. Prematurely discontinuing subjects had their last outcome measure carried forward. Efficacy outcome for 1-hr pad test data was collected at visit 5.

3. Results

3.1. Participants flow

A total number of 147 patients were screened for SUI during the study period. Eighty seven were excluded from the study because of different reasons (see Fig. 1). Sixty patients were subjected to preliminary investigations and randomly allocated to the test

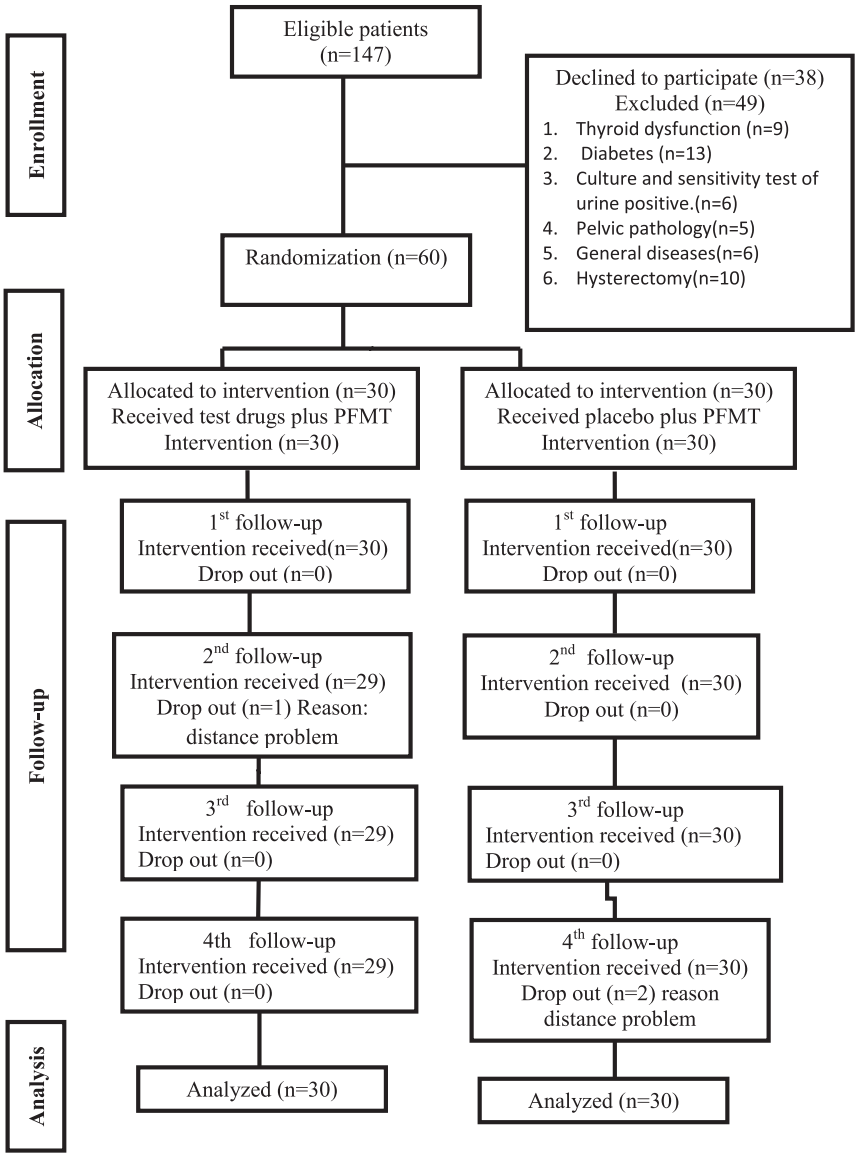

Fig. 1. Flow chart of participants according to consort statement.

($n = 30$) and control ($n = 30$) group allowing for 10% drop out. Details are summarized in Fig. 1.

3.2. Baseline characteristics

The baseline variables were comparable between groups (age, religion, diet, residence, height, weight, body mass index, duration of incontinence, incontinence episode frequency, amount of leakage, frequency of voiding in a day, age of menarche, age of marriage, duration of cycle, duration of flow and parity). There was no statistical difference in mean baseline measurements between the groups (Table 1).

3.3. Efficacy

The 1-hr pad test was positive in all patients at baseline. The SUI was alleviated in 18/30 (60%) and 11/30 (36.67%) patients in the test and control group respectively, showing approximately 23% greater improvement in the test group compared to control group (cure rate of test group − cure rate of control group). Between the group comparison was considered statistically significant ($P = 0.035$) (Table 2). The intra group comparison of one hour pad test was statistically significant in both groups ($P < 0.001$) for intervention compared to baseline.

3.4. Safety profile

All the biochemical parameters were comparable and statistically not significant when compared from baseline in both groups except SGPT ($P = 0.008$) in the test group which was statistically significant but laboratory values were within normal range. Alkaline phosphatase values between the groups was statistically significant ($P = 0.042$), however, it was within normal range (Table 3). Clinically, none of the patients reported any adverse effects in either group.

4. Discussion

4.1. Efficacy

In the present study, SUI was cured in 60% and 37% patients in the test and control group respectively. The test group showed

Table 1
Baseline characteristics of patients.

Characteristics	Test group ($n = 30$)	Control group ($n = 30$)	Total ($n = 60$)	P value
Age (y)	33.23 ± 5.929	36.03 ± 5.44		0.675
21–30	8(26.67)	6(20)	14(23.33)	
31–40	19(63.33)	19(63.33)	38(63.33)	
41–50	3(10)	5(16.67)	8(13.33)	
Religion				
Hindu	5 (16.67)	8(26.67)	13(21.67)	0.360
Muslim	25(83.33)	21(70)	46(76.67)	
Christian	0	1(3.33)	1(1.67)	
Residence				
Urban	24(80)	28(93.33)	52(86.67)	0.254
Rural	6(20)	2(6.67)	8(13.33)	
Diet				
Non-vegetarian	30 (100)	28(93.33)	58(96.67)	0.491
Vegetarian	0	2(6.67)	2(3.33)	
Duration of incontinence (y)	1.88 ± 2.15	1.36 ± 1.77		
≤1	19(63.33)	19(63.33)	38(63.33)	1.000
2–5	9(30)	10 (33.33)	19(31.66)	
6–10	2(6.67)	1(3.33)	3(5)	
Frequency of voiding in daytime	4.46 ± 0.50	4.46 ± 0.50		0.99
Incontinence episode frequency	2.36 ± 0.55	2.4 ± 0.54		0.77
Age of Menarche (y)	13.4 ± 1	13.23 ± 1		0.532
Age of Marriage (y)	18 ± 2.10	17.26 ± 1.23		0.140
Duration of cycle (day)	29 ± 1.533	29.03 ± 1.974		0.94
Duration of flow (day)	3.23 ± 0.81	3.13 ± 1.67		0.702
Height (cm)	1.52 ± 0.05	1.51 ± 0.04		0.518
Weight (kg)	63.78 ± 1.058	64.93 ± 93		0.665
Body mass index (kg/m^2)	27.49 ± 4.86	27.41 ± 4.21		0.946
Under wt	0	0	0	
Normal	9(30)	11(36.67)	20(33.33)	0.549
Over wt	12(40)	8(26.67)	20(33.33)	
Obesity	9(30)	11(36.67)	20(33.33)	

Data presented: Mean ± SD or No (%); $P > 0.05$, considered not significant.
Test used: Unpaired Student's '*t*' test for continuous measurement and Fisher exact/Chi-square tests for categorical measurements.

23%.greater improvement than the control group. This study is first of its kind carried out for this treatment so cannot be compared to previous studies. However, the results of the present study are comparable with a previous study carried out by Ghoniem et al., where combination therapy of duloxetine and PFMT in the treatment of women with SUI showed improvement in SUI of 54.5%, statistically significant ($P < 0.01$) compared with no treatment [11]. Another study showed 42% improvement in SUI with intraurethral injection of collagen [7]. The specific mechanism of action of these herbs are unknown; however, it has been theorized that these plant materials are probably effective through selective serotonin noradrenaline reuptake inhibitors (SNRIs) pathway as they are proven for anxiolytic, antidepressive or tranquilizing, and sedative properties [25].

B. serrata contains chemical constituents such as incensole acetate, acetyl 11-keto β-Boswellic acid (AKBA), 11-ketoβ-Boswellic

Table 2
Therapeutic outcome of the test and control group (One hour pad test).

Therapeutic outcome (1-h pad test)	Test group ($n = 30$)		Control group ($n = 30$)	
	Baseline (V1)	Post test (V5)	Baseline (V1)	Post test (V5)
Improved	0	18 (60)	0	11 (36.67)
Not improved	30	12 (40)	30	19 (63.33)
P value	<0.001		<0.001	

Data presented: No (%); $P < 0.001$, considered extremely significant. Between the group comparison, $P = 0.035$, considered significant; V1: Baseline visit and V5: Follow up visit at 8 weeks.
Test used: Chi-square test.

Table 3
Comparison of safety parameters in the test and control groups.

Variables	Period	Test group ($n = 30$)	Group B ($n = 30$)	P value
Hb	BL	11.19 ± 1.24	11.23 ± 1.244	0.905
	Post-test	11.34 ± 1.39	11.38 ± 1.45	0.984
	P value	0.550	0.501	
ESR	BL	30.26 ± 12.72	31.46 ± 12.56	0.712
	Post-test	28.73 ± 19.60	28.7 ± 19.48	0.992
	P value	0.720	0.394	
RBS	BL	97.83 ± 15.17	104.1 ± 15.67	0.121
	Post-test	104.5 ± 22.44	97 ± 16.14	0.148
	P value	0.189	0.085	
SGOT	BL	19.93 ± 5.31	19.96 ± 6.50	0.981
	Post-test	18.96 ± 5.22	21.36 ± 8.93	0.209
	P value	0.435	0.425	
SGPT	BL	22.16 ± 6.98	20.1 ± 7.56	0.266
	AT	18.03 ± 5.73	20.45 ± 10.95	0.286
	Post-test	0.008	0.878	
Alkaline phosphatase	BL	116.76 ± 24.49	127.56 ± 32.6	0.152
	Post-test	117.06 ± 22.19	134.03 ± 38.9	0.042
	P value	0.955	0.380	
Blood urea	BL	25.36 ± 6.72	25.26 ± 5.78	0.953
	Post-test	25.13 ± 6.12	27.46 ± 11.31	0.324
	P value	0.877	0.316	
S. creatinine	BL	0.80 ± 0.12	0.823 ± 0.10	0.459
	Post-test	0.85 ± 1.33	0.823 ± 0.11	0.351
	P value	0.073	0.999	

Data presented: Mean ± Standard Deviation; BL: Baseline; $P > 0.05$, Considered not significant.
Test used: Unpaired and paired '*t*' test.

acid (KBA), both volatile and non-volatile oils, tannins, phenolics and steroid substances. The most important constituents are Acetyl 11-Keto β-Boswellic Acid (AKBA) and 11-Ketoβ-Boswellic Acid (KBA). The composition of oleo-gum-resin is moisture, 10-11; volatile oil, 8-9; rosin, 45-50; gum, 30-34; and insol matter, 4–5% [26]. Previous researches has shown that *B. serrata* has antidepressive, anxiolytic [27], sedative, analgesic, neuroprotective [20], antioxidant, immunomodulatory, and antiinflammatory properties [28]. *C. scariosus* contains chemical constituents such as steroid, terpenoid, phenolics, tannin and resin. The tubers yield 0.5% of an essential oil; an additional (0.5%) oil has been obtained by acid hydrolysis of non volatile portion. Several volatile compounds including cuperine (15.8%), isopapatchoulene, selina-4(5) –en-3-one (16.5%), I-oxo-selina-4(14), 7(11)-diene, selina-4,(5), 7(11)-dien -12-ol and patchoulanol have been reported from the oil [29]. It also has antidepressive, inflammatory and antioxidant properties [30].

In conventional medicine, Duloxetine (commonly known for its anti psychotic use) was associated with significant improvements in SUI symptoms in several RCTs [31]. Duloxetine is thought to block the reuptake of serotonin and norepinephrine in Onuf's nucleus in the sacral spinal cord, there by activating pudendal motor neurons that increase the urethral striated muscle tone and the force of sphincter contraction. This increased sphincter activation prevents involuntary urine loss [32]. Moreover, pharmacological research has demonstrated efficacy of serotonin-norepinephrine reuptake inhibitors for both major depression and stress UI, and this has contributed to the question whether there are common biological underliers for both conditions. Thior et al., mentioned that several common biological and neurological underliers are possible; serotonergic pathways are linked to both the regulation of voiding function and depression [33].

Hence, the mechanism of action of these herbs can be compared with SNRIs. Kar and Menon found that the non-phenolic fraction of *B. serrata* resin distillation ether extraction showed sedative and analgesic effect in albino rats. The effects of Boswellia resin on the central nervous system have been discussed by Moussaieff and

Mechoulam. They used behavioral models and found that incensole acetate obtained from Boswellia resin exerted anxiolytic and antidepressive effects as well as a sedative effect. These findings were corroborated by an immune histochemical mapping of mice brains following incensole acetate administration [25]. To pursue a mechanism of incensole acetate's central effects, they examined incensole acetate for its binding to an array of related receptors, ion channels and transport proteins. Incensole acetate bound to none of the known pharmacological targets tested, but robustly activated the TRPV3 (transient receptor potential vanilloid) channel in several in-vitro assays: activated a calcium influx in HEK293 cells, and primary keratinocytes, as well as a TRPV3 current in HEK293 cells stably expressing TRPV3. They suggest that incensole acetate exerts anti-depressive and anxiolytic effects. It should be noted that the finding that incensole acetate exhibits its effects on the CNS via TRPV3 channels in the brain may suggest that this channel can perhaps be used as a novel pharmacological target for the amelioration of such disorders. Transient receptor potential (TRP) ion channels are widely distributed in various tissues, including peripheral neurons and the central nervous system (CNS). Incensole acetate constituent of *Boswellia* resin is currently the most potent specific modulator of the TRPV3 channel [27].

Ramesh et al., in their study showed that *C. scariosus* oil possesses antidepressant effects. They indicated that the pattern of behaviors exerted by the extract had similar effect to that of imipramine, and concluded that this effect might be related to inhibition of nor-epinephrine uptake which eventually leads to increased availability of nor-epinephrine in synapses [34].

Hence, in the present study, it is suggested that boswellia resin probably had effects on the CNS via TRPV3 channels in the brain and thought to block the reuptake of serotonin and norepinephrine in Onuf's nucleus in the sacral spinal cord, there by activating pudendal motor neurons that increase the urethral striated muscle tone and the force of sphincter contraction. *C. scariosus* is also proven for anti-depressive activity and had similar effect to that of imipramine.

In the placebo plus PFMT group the response was observed in 37 percent. The theoretical basis of physical therapies, for the treatment of physiotherapy, PFM dysfunction associated with SUI, is that facilitation and strengthening of the PFM may improve efficiency in the sphincteric action around the urethra and support pelvic organs. It has been suggested that a strong contraction of the PFM will 'clamp' the pressure rise in the urethra as it is pressed against the pubic symphysis. In addition, it seems that a PFM contraction in response to a rise in intra-abdominal pressure may prevent urethral descent. PFM training may also result in hypertrophy of the muscles, increasing the external mechanical pressure on the urethra, and improving structural support for the pelvic organs [35].

4.2. Safety profile

All the biochemical parameters were comparable and statistically not significant showing that the trial herbs were safe in the present study according to biochemical analysis of body fluids.

4.3. Strengths of the study

This study is the first of its kind, where a combination of *B. serrata* and *C. scariosus* was evaluated in SUI of reproductive age women. Additionally, it was randomized, single-blind, placebo-controlled study with good compliance. The biochemical laboratory investigations were with normal limits and no adverse effects were noted, which suggests safety of the test drugs. Secondly, the power of the study was 90% with level of significance 5%. Thirdly, objective parameter1-hr pad test was used.

4.4. Limitations and recommendations

The limitations of the present study were that it was single-blind, the treatment was only for 8 weeks and follow-up-assessment took place only once post-intervention. Double blind study could not be conducted due to lack of facility, infrastructure, resources and man power. It can be expected, that the efficacy will improve further, if the treatment is prolonged. Another limitation of this study was that it included only reproductive age women and other patients such as postpartum or menopause was excluded.

Therefore, future studies are needed to investigate the effect of trial drugs on stress urinary incontinence of aforementioned population.

Further, double-blind, phase III trials with longer duration of treatment and follow-up are recommended. Additionally, interventions are recommended to assess effectiveness of test drugs in urge or mixed incontinence and compare the effectiveness of trials drugs with other standard conservative therapies. The exact mechanism of action of these herbs and the specific molecule responsible for the efficacy of herbal combination on SUI is unclear; therefore, further studies are needed for investigation of their effect on serotonergic pathways.

5. Conclusion

The combination of *B. serrata* and *C. scariosus* plus PFMT was better than PFMT alone. Further studies are needed to find out the exact mechanism of action of these herbs.

Conflict of interest statement

None.

Acknowledgment

The authors are thankful to the Director and all staff at the National Institute of Unani Medicine and Dept of AYUSH, Ministry of Health and family welfare, GOI for providing their support in carrying this dissertation work. The authors are also thankful to the patients for their contribution in the study.

References

[1] Tsai YC, Liu CH. Urinary incontinence among Taiwanese women: an outpatient study of prevalence, comorbidity,risk factors, and quality of life. Int Urol Nephrol 2009;41(4):795–803.
[2] Kim JC, Chung BS, Choi JB, Lee JY, Lee KS, Park WH, et al. A safety and quality of life analysis of intravaginal slingplasty in female stress incontinence: a prospective, open label, multicenter, and observational study. Int Urogynecol J 2007;18(11):1331–5.
[3] Athanasopoulos A, Perimenis P. Pharmacotherapy of urinary incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2009;20(4):475–82.
[4] Shahali S, Kashanians M, Azari A, Salehi R. Effects of pelvic floor muscle exercises on quality of life outcomes inwomen with stress urinary incontinence. Med J Islamic Repub Iran 2010;24(3):159–62.
[5] Bakar Y, CinarOzdemir O, Ozengin N, Duran B. The use of extracorporeal magnetic innervation for the treatmentof stress urinary incontinence in older women: a pilot study. Arch Gynecol Obstet 2011;284:1163–8.
[6] Hong JH, Choo M, Lee K. Long-term results of laparoscopic burch colposuspension for stress urinary incontinence in women. Korean Med Sci 2009;24(6):1182–6.
[7] Kerr LA. Bulking agents in the treatment of stress urinary incontinence: history, outcomes, patient populations, and reimbursement profile. Rev Urol 2005;7(Suppl. 1):S3–11.
[8] Tannenbaum C, Brouillette J, Corcos J. rating improvements in urinary incontinence: do patients and their physicians agree? Age Ageing 2008;37(4):379–83.
[9] ter Meulen PH, Berghmans LC, Nieman FH, van Kerrebroeck PE. Effects of Macroplastique® implantation system for stressurinary incontinence and urethral hypermobility in women. Int Urogynecol J Pelvic Floor Dysfunct 2009;20(2):177–83.
[10] Nygaard IE. Stress urinary incontinence. Obstet Gynecol 2004;104:607–20.

[11] Ghoniem GM, Van Leeuwen JS, Elser DM, Freeman RM, Zhao YD, Yalcin I, et al. A randomized controlled trial of duloxetine alone, pelvic floor muscle training alone, combined treatment and no active treatment in women with stress urinary incontinence. J Urol 2005 May;173(5):1647–53.
[12] Ghani N. KhazinaulAdvia. New Delhi: IdaraeKitabusShifa; 2001. p.1069, 1070, 1302.
[13] Bhagwat D, Kharya MD, Bani S, Pandey A, Chauhan PS, Kour K, et al. *Cyperusscariosus* chloroform fraction inhibits t cell responses in Balb/C mice. Tropical J Pharm Res 2009;8(5):399–408.
[14] Singh GB, Atal CK. Pharmacology of an extract of salaiguggal ex-*Boswelliaserrata*, a new nonsteroidal anti-inflammatory agent. Agents Actions 1986;18: 407–12.
[15] Kafri R, Langer R, Dvir Z, Katz-Leurer M. Rehabilitation vs drug therapy for urge urinary incontinence: short-term outcome. Int Urogynecol J 2007;18: 407–11.
[16] Karantanis E, Fynes M, Moore KH, Stanton SL. Comparison of the ICIQ-SF and 24-hour pad test with other measures for evaluating the severity of urodynamic stress incontinence. Int Urogynecol J Pelvic Floor Dysfunct 2004;15(2): 111–6.
[17] Samuelsson EC, Victor FTA, Tibblin G, Syarddsudd Kurt F. Signs of genital prolapse in a Swedish population of women 20 to 59 years of age and possible related factors. Am J Obstet Gynecol 1999;180:299–305.
[18] Persu C, Chapple CR, Cauni V, Gutue S, Geavlete P. Pelvic organ prolapse quantification system (POP–Q) – a new era in pelvic prolapse staging. J Med Life 2011;4(1):75–81.
[19] Beiber EJ, Sanfilippio JF, Horowitz IR. Clinical gynecology. Canada: Churchill Livingstone; 2006. p. 377–410.
[20] Versi E, Cardozo L, Anand D. The use of pad tests in the investigation of female urinary incontinence. J Obstet Gynaecol 1988;8:270–3.
[21] Lose G, Versi E. Pad-weighing tests in the diagnosis and quantification of incontinence. Int Urogyneeol J 1992;3:324–32.
[22] Tchou DCH, Adams C, Varner RE, Denton B. Pelvic-floor musculature exercises in treatment of anatomical urinary stress incontinence. Phys Ther 1988;68: 652–5.
[23] Price N, Dawood R, Jackson SR. Pelvic floor exercise for urinary incontinence: a systematic literature review. Maturitas 2010;67(4):309–15.
[24] Castro-Diaz D, Palma PCR, Bouchard C, Haab F, Hampel C, Carone R. Effect of dose escalation on the tolerability and efficacy of duloxetine in the treatment of women with stress urinary incontinence. Int Urogynecol J 2007;18:919–29.
[25] Moussaieff A, Mechoulam R. Boswellia resin: from religious ceremonies to medical uses; a review of in-vitro, in-vivo and clinical trials. JPP 2009;61: 1281–93.
[26] Anonymous. The wealth of India, vol. 2. New Delhi: Council of Scientific and Industrial Research; 1988. p. 203–9.
[27] Moussaieff A, Rimmerman N, Bregman T, Straiker A, Felder CC, Shoham S. Incensole acetate, an incense component, elicits psychoactivity by activating TRPV3 channels in the brain. FASEB J 2008;22:3024–34.
[28] Upaganlawar A, Ghule B. Pharmacological activities of *Boswellia serrate* Roxb – mini review. Ethnobot Leafl 2009;13:766–74.
[29] Anonymous. The wealth of India, vol. 2. New Delhi: Council of Scientific and Industrial Research; 2001. p. 334.
[30] Ross IA. Medicinal plants of the world. 2nded., vol. 1. New Jersey: Humana Press; 2003. p. 209–26.
[31] Basu M, Duckett JR. Update on duloxetine for the management of stress urinary incontinence. Clin Interv Aging 2009;4:25–30.
[32] Deepak P, Kumar TN. Duloxetine- pharmacological aspects. Int J Biol Med Res 2011;2(2):589–92.
[33] Felde G, Bjelland I, Hunskaar S. Anxiety and depression associated with incontinencein middle-aged women: a large Norwegiancross-sectional study. Int Urogynecol J 2012;23(3):299–306.
[34] Ramesh S, Rao BM, Mahesh V, Prabhaker T, Swamy P, Nagaraju P. Pharmacological study of anti-depressant like activity of *Cyperusscariosus*oil in mice. Int Res J Pharm App Sci 2012;2(5):139–42.
[35] Berghmans LC, Hendriks HJ, De Bie RA, Vanwaal wijk Vandoorn ES, BO K, Van Kerrebroeck PH. Conservative treatment of urge urinary incontinence in women: a systematic review of randomized clinical trials. BJU Int 2000;85: 254–63.