Original Research Paper Medical Science

# Development And Testing of New Herbal Ointment for the Treatment of Stress Urinary Incontinence-A Preliminary Study

**Oreščanin Višnja** ORESČANIN Ltd., A. Jakšića 30, 10000 Zagreb, Croatia

**Findri Guštek Štefica** Findri-Guštek Centre for gynecology, urology and occupational medicine, Ninska 5, Sesvete, Croatia

**ABSTRACT**

*The purpose of this work was development, formulation and testing of new herbal ointment for the treatment of stress urinary incontinence and its related symptoms. 50 women in the age range from 36 to 73 years were treated 8 weeks with vaginal ointment (2 g/day) which consisted of the following ingredients: oil macerates of the plants Capsella bursa-pastoris, Urtica diodica, Quercus robur, Quercus infectoria, Corylus avellana, Ocimum basilicum, Salvia officinalis, Achillea millefolium, Calendula officinalis, Matricaria chamomilla, Hypericum perforatum, Alchemilla vulgaris, Thymus serpyllum, Plantago major, Symphytum officinale; essential oils of the plants Melaleuca alternifolia, Cymbopogon martinii, Cinnamomum camphora ct. cineol, Eugenia caryophylata, Thymus vulgaris ct. tymol, Origanum vulgare; honey; glycerin and Cera flava. The degree of incontinence and its impact on the quality of life prior and after the therapy was assessed by the International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SF), where maximum score of 21 represents permanent incontinence and 0 no leakage of urine. Sexual gratification was assessed by the Pelvic organ prolepses / urinary Incontinence / Sexual Questionnaire (PISQ-12). The variables with the highest, statistically significant influence onto degree of incontinence and its impact on the quality of life were were Urine leak and related symptoms, Menopause, Frequent urinary tract infections, Age and Number of childbirth. Significant improvement concerning both, incontinence ($p<0.0001$) and sexuality ($p<0.0003$) was observed following two weeks of the application. In the end of the study the mean value of ICIQ-UI score decreased from 10.3±4.2 to 1.1±1.0 while PISQ-12 increased from 21.0±2.9 to 28.4±3.2. Following the eight weeks of the therapy 66% of the patients were completely dry, while other 34% exhibited only slight problems (ICIQ-UI score range 1-3). After only 7 days of the application the symptoms like burning, vaginal discharge, vaginal dryness and painful sexual intercourse decreased significantly while in the end of the treatment disappeared completely.*

**KEYWORDS : herbal ointment, stress urinary incontinence, olive oil extracts, medicinal plants, essential oils**

## INTRODUCTION

The International Continence Society Standardization of Terminology of Lower Urinary Tract Dysfunction established clinical definition of stress urinary incontinence (SUI) as the complaint of involuntary leakage during effort or exertion, or on sneezing or coughing (Luber, 2004). Its prevalence ranged between 4% and 35% depending on the country with age, obesity, and smoking as the most significant risk factors (Luber, 2004). Nygaard and Heit, 2004 reported that SUI occurs at least weekly in one third of adult women. Among 20,000 Chinese women in the age range from 20 to 99 years the prevalence of SUI was 18.9% (Zhu et al., 2009) and the significant risk factors are age, vaginal delivery, multiparty, alcohol consumption, central obesity constipation, chronic pelvic pain, history of respiratory disease, gynecological events, pelvic surgery, and perimenopause and postmenopause status. Among 1700 French women employed in academic hospital, 12.4% of them reported SUI (Peyrat et al., 2002). The pregnancy, particularly previous vaginal delivery and hysterectomy represented the significant risk factors. The prevalence of SUI reported by Minassian et al., 2008 among 2,875 adult women was 23.7%. The obtained significant risk factors were age, ethnic background, weight, parity and hysterectomy. Among 83,355 American nurses at the age range from 37 to 54 years 43% of them reported incontinence. Identified risk factors were age, race/ethnicity, body mass index, parity, smoking, type 2 diabetes mellitus, and hysterectomy (Danforth et al., 2006). A world wide survey conducted by McPhil, 2004 reviled the highest percentages of women with SUI in UK (41%) and Canada (42%) and the lowest percentage was obtained in Spain (23%) while the mean value for all tested countries was 32%. Two-thirds of the symptomatic women were younger than 50. Higher prevalence of SUI (Brown, et al., 1999) was obtained among postmenopausal women (56%).

The most common treatment aproaches are pelvic floor muscle training pelvic floor muscle training, bladder training, vaginal devices, and urethral inserts. Better results were obtained by surgical treatment. However, those methods were associated with more risk compared to the conventional treatment (Nygaard and Heit, 2004).

The purpose of this work was development, formulation and testing of new herbal ointment for the treatment of stress urinary incontinence and its related symptoms as posible alternative to conventional or surgical methods.

## MATERIALS AND METHODS

### Study Design

Among 437 patients in the age range from 18 to 78 reported to the center during October 2015th, 184 had the symptoms of urinary incontinence (UI). All the patients signed informed consent and completed three questioners. Among 184 incontinent patients, stress urinary incontinence (SUI) was confirmed in 98 of them. Those patients were subjected to Pap test, cervical swabs for the presence of aerobic bacteria, yeasts, *Ureaplasma urealyticum, Chlamydia trachomatis, Mycoplasma,* and hrHPV DNA. The sample preparation and analysis was described in details in our previous work (Findri Gustek et al., 2012). The patients with confirmed cervical lesions or bacterial/yeasts/viral infections were withdrawn from the study and subjected to conventional treatment depending on the diagnosis. The pregnant patients were also excluded. After all exclusions the rest of the 50 patients represented our target group. The patients were treated with herbal ointment (2 g/day) for eight weeks. The ointment was inserted deep into vagina before bedtime. The patients were advised to make daily notes about all the changes occurred during the course of the therapy. The interview of each patient was done twice a month. The degree of incontinence and its impact on the quality of life prior and after the therapy was assessed by the International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SF), where maximum score of 21 represents permanent incontinence and 0 no leakage of urine. The results of the ICIQ-UI SF may be divided into the following four severity categories: slight (1-5), moderate (6-12), severe (13-18) and very severe (19-21). Sexual gratification was assessed by the Pelvic organ prolapses / urinary Incontinence / Sexual Questionnaire (PISQ-12).

### Preparation of the Ointment

For the production of the macerate the following plants were used: *Capsella bursa-pastoris* (10%), *Urtica diodica* (10%), *Quercus robur* (10%), *Quercus infectoria* (10%), *Corylus avellana* (10%), *Ocimum basilicum* (10%), *Salvia officinalis* (10%), *Achillea millefolium* (10%), *Calendula officinalis* (5%), *Planta-*

*go major* (5%), *Matricaria chamomilla* (2%), *Hypericum perforatum* (2%), *Alchemilla vulgaris* (2%), *Thymus serpyllum* (2%), *Symphytum officinale* (2%). The macerate was prepared from the dried plants obtained from herbal pharmacy and extra virgin olive oil with solid/liquid ratio = 1:5. The plants were macerated 30 days on 50°C and filtered. 80% of the macerate was mixed with 4.3% of chestnut honey and 5% of glycerin and the mixture was heated to 80°C. 10% of melted *Cera flava* was added into the mixture, homogenized and heated for additional 10 minutes and allowed to cool to the room temperature. The essential oils of *Melaleuca alternifolia* (0.2%), *Cympobogon martini* (0.1%), *Thymus vulgaris* (0.1%), *Eugenia caryophylata* (0.1%), *Cinnamomum camphora* (0.1%) and *Origanum vulgare* L (0.1%) were added into cooled mixture, mixed thoroughly and packed.

**Statistical Analysis**

For statistical evaluation Statistica 11.0 software package was employed. The description of the treated population was done by basic statistics and frequency tables. Statistical significance was set to $p<0.05$ in all the tests performed. The differences in the percentage of each parameter between prior and after the therapy were assessed by $\chi^2$ test. The influence of the predictor variables on the degree of incontinence was tested by Multiple regression method (Orescanin et al., 2015a).

## RESULTS AND DISCUSSION

**Description of the Population**

The study group ranged from 36 to 73 years (54.68±10.89) with the highest percentage of women (28%) ranging from 51 to 60 years. Equal distribution was obtained in the groups ranging from 41 to 50 years and 61 to 70 years (20%) while the women younger than 40 and older than 70 were represented with 18% and 10%, respectively.

According to the education level, 60% of the patients finished secondary school, 16% primary school while 10%, 12% and 2% of them had higher education, university diploma and PhD, respectively.

Postmenopausal women represented 64% of the population (Table 1). Among the tested population 88% of them had at least one childbirth. The women with two childbirths prevailed (42%) followed by three births (26%). 9 of 50 patients had one or two miscarriages and 11 (18%) of them had 1 to 3 induced abortions (22%).

Frequent gynecological problems were reported by 62% of the participants (Table 1). Among them the problems like inflammation, burning, vaginal discharge, unpleasant odor, vaginal dryness, painful sexual intercourse, and frequent infections prevailed.

Frequent urinary tract infections persisted in 44% of the patients (Table 1). Urine leakage, frequent urination, urine retention, dysuria, pain and burning prevailed among incontinence symptoms.

ICIQ-UI SF score ranged from 3 to 16 (10.25±4.19). Among them 20% had slight problems, 40% of them reported moderate and other 40% severe incontinence problems. According to the results of multiple regression analysis ICIQ-UI SF score showed statistically significant correlation with selected predictor variables ($R = 0.79$; $p<0.0027$). Among the variables with the highest, statistically significant correlations were Urine leak and related symptoms (p=0.0015), Menopause (p=0.0123), Frequent urinary tract infections (0.0382), Age (0.0418) and No. of childbirth (0.0481).

Incontinence problems combined with the vaginal dryness and painful intercourse had also significant impact on the sexual gratification. PISQ-12 score before the therapy (Fig. 2) ranged from 14 to 26 (21±2.91). The results of Multiple regression analysis reviled significant correlation between predictor variables and PISQ-12 score ($R = 0.88$; $p<0.0381$). ICIQ-UI SF score (p=0.0021), Urine leak and related symptoms (p=0.0104), Menopause (p=0.0372), Gynecological problems (p=0.0414) and age (p=0.0448) had statistically significant contribution. Those results confirmed that urinary incontinence had highly significant impact on the quality of sex life.

**Table 1. Frequencies tables for selected categorical variable of the tested population**

| Variable | Category | N | % |
|---|---|---|---|
| Menopause | Yes | 32 | 64 |
| | No | 28 | 36 |
| No. of childbirth | 0 | 6 | 12 |
| | 1 | 6 | 12 |
| | 2 | 21 | 42 |
| | 3 | 13 | 26 |
| | 5 | 2 | 4 |
| | 8 | 2 | 4 |
| No. of miscarriages | 0 | 41 | 82 |
| | 1 | 3 | 6 |
| | 2 | 6 | 12 |
| No. of induced abortions | 0 | 39 | 78 |
| | 1 | 6 | 12 |
| | 2 | 3 | 6 |
| | 3 | 2 | 4 |
| Gynecological problems | No | 31 | 62 |
| | Yes | 19 | 38 |
| Frequent urinary tract infections | Yes | 22 | 44 |
| | No | 28 | 56 |
| Urine leakage and other symptoms | No | 0 | 0 |
| | Yes | 50 | 100 |

**The Outcome of the Therapy**

The first signs of the improvement in the case of incontinence appeared after 7 days of the treatment with the herbal ointment. The improvement was reflected in the lower number of urination during the day and night, the possibility of complete emptying of the bladder half an hour after the application of the ointment, ability to retain the urine much longer, lower volume and frequency of the escaped urine during coughing, sneezing and physical activity and pleasant feeling of vaginal lubrication.

As presented in Fig. 1 ICIQ-UI SF score decreased almost linearly during the course of therapy with the value of 7.2±1.8 after two weeks, 4.3±1.5 after four weeks, 2.7±1.4 following the 6 weeks and finally 1.1±1.0 in the end of eight week. Significant difference was found between the mean value of ICIQ-UI SF score before the therapy and each follow up period since P value were in all cases <0.0001. In the end of the therapy 66% of the patients were completely dry while in other 34% of them only slight discomfort persisted with ICIQ-UI SF score ranged from 1-3.

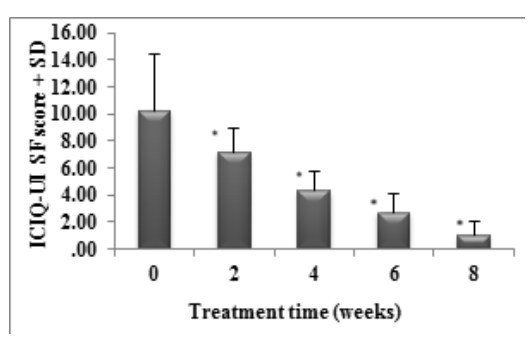


**Figure 1. The results of International Consultation on Incontinence Questionnaire - Urinary Incontinence Short Form (ICIQ-UI SF) prior and after each follow up period.*-statistically significant at p<0.05**

Multiple regression analysis showed no obvious, statistically significant contribution of the predictor variable to the outcome of the therapy expressed as ICIQ-UI SF score (R=0.60; p=0.1571). None of the tested predictor variable showed statistically significant contribution.

PISQ-12 score was significantly higher for each follow up period (Fig. 2) compared to the period before the therapy ($p<0.0001$) which pointed out to the improvement in sexual gratification.

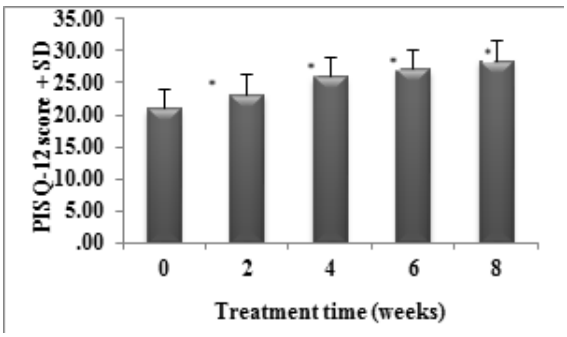


**Figure 2. The results of Pelvic organ prolepses / urinary Incontinence / Sexual Questionnaire (PISQ-12) prior and after each follow up period.*-statistically significant at p<0.05**

The mean values increased from 23.2±3.0 after two weeks of the therapy to 28.4±3.2 in the end of the treatment period. Linear regression showed excellent correlation between the ICIQ-UI SF and PISQ-12 scores ($R^2$=0.998; p<0.00001) during the course of the therapy confirming once again a significant influence of incontinence on the sexual gratification. The symptoms and problems like vaginal dryness, inflammation, burning, vaginal discharge, painful intercourse, and unpleasant odor disappeared completely in the end of the therapy. Gynecological examination also confirmed significant improvement in the appearance of vaginal mucosa in postmenopausal women following the therapy.

Significant improvement following the therapy could be explained by the composition of the ointment containing the plants like *Capsella bursa-pastoris* and *Urtica diodica* that induced contraction of smooth muscles (Al-Snafi, 2015; Grosso et al., 2011; Broncano et al., 1987), and consequently, enhanced both bladder and uterine muscle tonus significantly.

The bioactive components extracted from the plants with confirmed uterotonic activity (*Matricaria chamomilla*, *Calendula officinalis*, *Plantago major*, *Symphytum officinale*, *Capsella bursa pastoris,* and *Hypericum perforatum*) also contributed to the improvement of uterine muscle tonus (Shipochliev, 1981).

Besides, the tannins rich plants with well known astringent activity like *Quercus robur*, *Quercus infectoria*, *Corylus avellana*, *Ocimum basilicum* had also positive effect on vaginal mucosa trough their strong wound healing, anti-inflammatory and antioxidative potential (EMA, 2009; Ahmad et al., 2011; Oliveira et al., 2007; Dubey and Pathak, 2015).

Beneficial effects of the oil extracts of the plants *Salvia officinalis*, *Achillea millefolium Calendula officinalis*, *Plantago major*, *Matricaria chamomilla*, *Hypericum perforatum*, *Alchemilla vulgaris*, *Thymus serpyllum* and *Symphytum officinale* onto vaginal mucosa was described in details in our previous papers (Orescanin et al., 2015a, Orescanin et al., 2015a, Orescanin and Findri Gustek, 2015c). In short, the selected plants act in the formulation as free radical scavenging, metal chelating, and reactive oxygen quenching agents, thus protecting vaginal mucosa from the damage caused by highly reactive species present in intracellular space. The main wound healing and anti-inflammatory mechanism could be explained by interaction of bioactive components of the extracts with host membrane signaling pathways that promote the synthesis of collagen fibers and anti-inflammatory proteins trough numerous cascade reactions. Consequently, it results with wound closure and re-epithelization of the damaged area and decrease of inflammatory changes of the vaginal mucosa. Another anti-inflammatory mechanism could be explained by the inhibition of host membrane signaling pathways, and consequently the inhibition of the synthesis of pro-inflammatory mediators. Furthermore, the above mentioned plants macerate in the combination with essential oils of *Melaleuca alternifolia*, *Thymus vulgaris*, *Cymbopogon martinii*, *Origanum vulgare*, *Cinnamomum camphora* and *Eugenia caryophyllata* showed a strong antibacterial, antifungal and antiviral activity against wide range of genital pathogens. So, they maintain the healthy balance of very complex vaginal flora by preventing uncontrolled growth of the pathogens that can cause infection and also serve as natural preservatives in the ointment (Orescanin and Findri Gustek, 2015c).

Honey with its antimicrobial, prebiotic and probiotic activity provides healthy balance of the vaginal flora by preventing the transition of the vaginal flora from comensal to pathogenic form. It encourages the development of normal vaginal flora and establishes normal acidic pH of the vagina (Orescanin and Findri Gustek, 2015c).

*Cera flava* was used in the ointment formulation as supporting material and also as the component which forms protective layer on the genital tract membranes and prevent irritations while glycerol was used in the ointment formulation as moisturizer (Orescanin and Findri Gustek, 2015c).

## CONCLUSIONS

The prevalence of stress urinary incontinence among the women reported to the center was 22.4%. The most frequent symptoms/conditions prior to the therapy were: frequent urination (up to 30 times per day), inability to sustain urine, urine retention, frequent bladder infections, vaginal dryness, painful intercourse, loss of sexual desire. The variables with the highest, statistically significant influence onto degree of incontinence and its impact on the quality of life were were Urine leak and related symptoms, Menopause, Frequent urinary tract infections, Age and No. of childbirth. Significant improvement concerning both, incontinence ($P < 0.0001$) and sexuality ($P < 0.0003$) was observed following two weeks of the application. In the end of the study the mean value of ICIQ-UI score decreased over 9 times while PISQ-12 increased for app. 1.4 times. In the end of the therapy 66% of females had no leakage of urine, while other 34% exhibited only slight symptoms (mean ICIQ-UI score = 1.1; range 1-3). After only 7 days of the application the symptoms like burning, vaginal discharge, vaginal dryness and painful sexual intercourse decreased significantly while in the end of the treatment disappeared completely.

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