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# Clinical study of effectiveness and safety of CELcomplex® containing Cucurbita Pepo Seed extract and Flax and Casuarina on stress urinary incontinence in women

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ABSTRACT

*Aim:* The safety and effectiveness of a preparation containing a mix of Cucurbita Pepo Seed extract, Equisetum arvense and Linum usitatissimum - Flax A (CELcomplex®) on stress urinary incontinence (SUI) was evaluated in female patients recruited from 20 urological and gynaecological outpatient clinics in Slovakia.

*Methods:* A total of 86 women aged from 32 to 88 with SUI (grade 1 = 44, grade 2 = 42) were enrolled in the study and followed-up for six weeks (point 1) and twelve weeks (point 2). The primary outcome of the study was evaluated by changes in day-time and nocturnal urinary frequency (bathroom visits) and urinary incontinence episodes (leaks). Also, adverse events were quantified as well as the self-perceived effectiveness of the treatment. Research Ethics Board approval was obtained for this study.

*Results:* After 12 weeks of treatment there was a 30% (grade 1 SUI, $p < 0.01$), and 35% (grade 2 SUI, $p < 0.01$) improvement in urinary incontinence episodes, a 40% (grade 1 SUI, $p < 0.01$) and 26% (grade 2 SUI, $p < 0.01$) improvement in day-time urination frequency and 64% (grade 1 SUI, $p < 0.01$) and 54% (grade 2 SUI, $p < 0.01$) improvement in nocturnal urinary frequency. Reported side effects were: headache (3.5%), flatulence (4.1%) and gastrointestinal discomfort (3%). A total of 89.4 % of women in the study reported no side effects from this therapy and 97% acknowledged improvement of symptoms.

*Conclusion:* This clinical study demonstrated that a 12 week treatment with a mix of Cucurbita Pepo Seed extract, Equisetum arvense and Linum usitatissimum - Flax A (CELcomplex®) is highly effective on stress urinary incontinence (SUI) with minimum adverse events. Further studies may be needed in order to determine the effectiveness and efficacy of this phytotherapy in other populations.



## 1. Introduction

The International Continence Society (ICS) defines stress urinary incontinence (SUI) as the complaint of any involuntary leakage, which is associated with increased abdominal pressure and insufficient urethral sphincter mechanism.[32] The main symptom of stress urinary incontinence is the involuntary loss of urine on exertion, sneezing or coughing.

Epidemiological research has revealed several factors associated with urinary incontinence in women. It is caused by obesity, aging, childbirth[32] and by a weakening of the bladder sphincter and pelvic floor muscles.[10] Modifiable risk factors have not been investigated to the same extent, and several of the studies that do address such factors do not control adequately for confounders.[12] In women, risk factors for SUI include multiple or complex vaginal deliveries, high infant birth weight, a history of hysterectomy, and physiological

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**Abbreviations**

| | |
|---|---|
| SUI | stress urinary incontinence |
| UI | urinary incontinence |
| ICS | The International Continence Society |
| SD | standard deviation |
| OAB | overactive bladder |
| GIT-D | gastrointestinal discomfort |

changes related to the transition to postmenopause. Smoking, a high body mass index, and constipation are also associated with an increased risk of SUI.[8,27,28,2,14,7]

Urinary incontinence affects almost 50% of middle-aged and older women and significantly impacts quality of life and accounts for more than $30 billion in annual direct costs in the United States.[25] There is a clear dose-response effect of weight on urinary incontinence, with each 5-unit increase in body mass index associated with a 20%–70% increase in risk of urinary incontinence.[31] Former and current heavy smoking (more than 20 cigarettes per day) is associated with any degree of incontinence while severe incontinence was weakly associated with smoking regardless of the number of cigarettes.[12] Physical activity is a modifiable risk factor with a potential for both positive and negative effects on SUI. The proportion of women reporting incontinennce disorder increased incrementally with age since roughly 7% of women between ages 20 and 39 report moderate or severe incontinence, and over 23% of women between ages 60 and 69 suffer from this condition.[21,22]

No medications have been approved for the treatment of SUI in the U.S and only one - duloxetine (Cymbalta, Eli Lilly) have been approved in Europe. Duloxetine, a dual serotonin–norepinephrine reuptake inhibitor is indicated only for the treatment of depression and neuropathic pain in the U.S.[8] Duloxetine is believed to influence neurotransmitters on the pudendal nerve. As a result, urethral sphincter contractions are strengthened, and the increased urethral closure forces prevent urine leakage.[18,26,33] In clinical trials, duloxetine has reduced incontinence episodes by 50% or more and has increased the quality of life in women with SUI. Side effects leading to discontinuation included dry mouth, fatigue, nausea, constipation, and hyperhidrosis. In studies, treatment-related nausea was noted in up to 40% of patients; in most of these patients, nausea occurred early during treatment, was transient, and of mild to moderate severity.[16,3,30,23]

The seeds and oil from pumpkin seeds have been used for many years for the relief of difficulties associated with an enlarged prostate gland and micturition problems related to irritable bladder.[17] The pumpkin seeds yield approximately 50% oil, (mostly linoleic and oleic acid and tocopherol), but the main active constituents are sterols (avenasterol, spinasterol) and sterol (sitosterol, stigmasterol).[1] The advantage of pumpkin seeds treatment arises from its tonic influence on the bladder and sphincter relaxation (EMA/HMPC/136022/2010). Pumpkin seed extract has beneficial activity in two ways: one on the hormonal level by inhibiting 5-alpha reductase an enzyme involved in hormone metabolism, resulting in anabolic and muscle strengthening effects; and a direct muscle relaxing effect resulting in a decreased urination frequency of the bladder.[24] Cucurbita pepo has many other indications approved by the European Medicine Agency (EMA/HMPC/136022/2010) such as benign prostatic hyperplasia, strength bladder function and enlarged prostate. The Equisetum arvense is traditionally used globally in urinary tract diseases. The Linum usitatissimum has a long history of medicinal use and its main effects are laxative, expectorant and inflammation of urinary organs among others.

The aim of the present study was to investigate the efficacy a 12 weeks treatment with CELcomplex® (a mix of Cucurbita Pepo Seed extract, Equisetum arvense and Linum usitatissimum - Flax A) on urinary incontinence episodes (daytime and nocturnal frequency of urination) and its safety (adverse events) in women with a diagnosis of stress incontinence grade I and II.

## 2. Materials and methods

### 2.1. Subjects and study design

A total of 86 female volunteers (stress incontinence grade 1 = 44, aged 32–88; stress incontinence grade 2 = 42, aged 34–79) from 20 urological and gynaecological outpatient departments in Slovakia were enrolled in this twelve week clinical study (point 1–6 week; point 2–12 week) and all 86 female volunteers complete the study. In group stress incontinence grade 1 and grade 2 were not the women with any histories of gynaecologic surgery (total/subtotal hysterectomy).

The treatment consisted of two pills of INCOVENAL® Comfort (CEL complex®, Vitamin $D_3$, magnesium and Vitamin C) (company VULM, Slovakia) for the first 14 days and then 1 pill daily until the end of the 12th week. The CELcomplex® 625 mg consisted of extracts Cucurbita Pepo Seed Extract, Equisetum arvense and Linum usitatissimum. In our study all women were instructed with Kegel exercises program.

Including criteria this biomedical research were:
1. Stress incontinence (grade 1, grade 2) without drugs therapy (duloxetine)
2. Incontinence pads or pants (small, normal, medium) (in Slovak contribution of the health insurance)
3. Good compliance – personal doctor's experience

Excluding criteria this biomedical research was:
1. Non-compliance women
2. No second visit after six weeks (the women need the second box of product)

All protocols in this study were approved by the Ethical Committee of Bratislava, Slovakia and written informed consent was obtained from all participating subjects. Demographic and medical data were obtained from the medical records and interviews conducted at study entry.

### 2.2. Diagnosis and evaluation of SUI

Participating urologists and/or gynaecologists diagnosed stress urinary incontinence and its grade according to the European Association of Urology. The urologists and/or gynaecologist diagnosed the stress urinary by standard medical care for stress urinary, if it was necessary (uncomplicated stress urinary incontinence). The subjects completed the first part of a questionnaire to evaluate the frequency of urinary incontinence episodes (leaks), daytime and nocturnal urinary frequency (times to the bathroom). A second part of the questionnaire was administered after the sixth week and after the 12th week they fulfilled the third part. Day time and nocturnal urinary frequency as well as urinary incontinence episodes were assessed at baseline, week 6 and week 12. Safety and tolerability was measured based on frequency of side effects. Also self-perceived effectiveness of the treatment was evaluated by each individual participant.

### 2.3. Statistical analysis

Values are expressed as means ± standard deviation (SD). Demographic variables were compared in order to determine differences among study groups (grade 1 and 2). Statistical analysis was conducted by comparing each study outcome (urinary incontinence, daytime and nocturnal urinary frequency) using a paired t-test approach for a level of significance of 5%. (*$p < 0.05$), (**$p < 0.01$).

## 3. Results

All female participants enrolled in this clinical study were diagnosed with stress incontinence grade 1 or grade 2 with or without overactive bladder (OAB) (grade 1 = 44–1 with OAB; grade 2 = 42–1 with OAB). The characteristics of the enrolled women are summarized in Table 1. The number of women after menopause was significantly higher in Grade 2 SUI compared to the less severe Grade 1 group ($p < 0.05$).

Frequency improvement of urinary incontinence episodes, day time and nocturnal urinary frequency.

Urinary incontinence episodes, diurnal and nocturnal urinary frequency was captured using a questionnaire at weeks 6 and 12 during treatment. The baseline values (before treatment) for frequency of urinary incontinence episodes (leaks), day time and nocturnal urinary frequencies was compared to the average values after six and twelve weeks of treatment. The number of incontinence episodes was significantly reduced from baseline levels by 19 % and 20% in grade 1 and grade 2 groups respectively after 6 weeks of treatment ($p < 0.05$) (Table 2). After week 12, the frequency of urinary incontinence episodes further decreased by 30 and 35 % compared to baseline in groups 1 and 2 respectively ($p < 0.01$). Moreover, as shown in Table 2, daytime and nocturnal urinary frequency also showed a statistically significant reduction from baseline at week 6 in the grade 1 SUI group (22% and 39% respectively in grade 1 SUI, $p < 0.05$). However, in the grade 2 SUI group, the reduction in daytime and nocturnal urinary frequency was not statistically significant at week 6. After 12 weeks of treatment, both groups experienced a significant reduction in both daytime and nocturnal urinary frequencies (40% and 64% respectively for grade 1 SUI and 26 and 54% respectively for grade 2 SUI, $p < 0.01$).

**Table 1**
Characteristics of women in the clinical study.

| | Grade 1 SUI (n = 44) | Grade 2 SUI (n = 42) |
|---|---|---|
| Age (years) | 51 ± 12 | 56 ± 11* |
| Body mass index (kg/m$^2$) | 27 ± 5.8 | 28 ± 4.9 |
| Number of childbirth | 1.7 ± 1.0 | 2.00 ± 0.9 |
| Smoker (%) | 89% none/11% yes | 94% none/6% yes |
| Menopause (%) | 71% none/29% yes | 56% none/44% yes* |

Values are expressed as average ± standard deviation (SD), *$p < 0.05$.

### 3.1. Safety and self-perceived efficacy

Adverse events after treatment with the mix of Cucurbita Pepo Seed extract, Equisetum arvense and Linum usitatissimum - Flax A (CELcomplex®) were captured in a questionnaire at week 12. The most common adverse events in both groups were headache (3.5%), flatulence (4.1%) and gastrointestinal discomfort (GIT-D) (2.9 %). The results are shown in the Table 3. A total of 89.4 % of women in the study reported no side effects during the 12 weeks of treatment.

A total of 97 % of participating women in the study reported a self-perceived improvement on incontinence episodes and day time and nocturnal urinary frequency (Table 3). There was no significant difference between groups. The clinical study showed the efficacy and the safety of treatment with CELcomplex®.

## 4. Discussion

The objective of this clinical study was to determine the effectiveness and safety of CELcomplex® containing Cucurbita Pepo Seed Extract, Flax and Casuarina on Stress Urinary Incontinence in women. As previously described, one of the major risk factors is age. In our clinical study we had two groups of stress incontinence women (grade 1 mean age 51 ± 12 vs. grade 2 mean age 56 ± 11 years). Danforth et al.[7] had in their study mean age 44.8 and self-reported incontinence was highly prevalent - 43% of women

**Table 2**
The characteristics of the improvement of urinary incontinence in the clinical study.

| | Grade1 | | | Grade 2 | | |
|---|---|---|---|---|---|---|
| | Baseline | Week 6 (Improvement %) | Week 12 (Improvement %) | Baseline | Week 6 (Improvement %) | Week 12 (Improvement %) |
| Daily frequency of incontinence episodes (leaks) | 2.9 ± 0.4 | 2.4 ± 0.2* (19 %) | 2.1 ± 0.2** (30 %) | 3.9 ± 0.4 | 3.1 ± 0.2* (20 %) | 2.5 ± 0.2** (35 %) |
| Daytime urinary frequency (times to the bathroom) | 4.6 ± 0.4 | 3.6 ± 0.3* (22 %) | 2.7 ± 0.2** (40 %) | 4.5 ± 0.5 | 4.0 ± 0.2 (12 %) | 3.4 ± 0.2** (26 %) |
| Nocturnal urinary frequency (times to the bathroom) | 2.3 ± 0.4 | 1.5v0.2* (39 %) | 0.8 ± 0.2** (64 %) | 2.51 ± 0.34 | 2.1 ± 0.2 (16 %) | 1.2 ± 0.1** (54 %) |

Values are expressed as average ± standard deviation (SD), (*$p < 0.05$), (**$p < 0.01$).

**Table 3**
The Adverse events after treatment with CELcomplex® in the clinical study.

| Adverse events | Grade 1 | | Grade 2 | | Total (average) |
|---|---|---|---|---|---|
| | 6 week (%) | 12 week (%) | 6 week (%) | 12 week (%) | |
| Headache | 4.5 | 4.5 | 2.4 | 2.4 | 3.5 |
| Flatulence | 4.5 | 4.5 | 4.8 | 2.4 | 4.1 |
| GIT-D | 4.5 | 0.0 | 2.4 | 4.8 | 2.9 |
| no side effects | 86.5 | 91.0 | 90.0 | 90.0 | 89.4 |
| Benefits | 100.0 | 100.0 | 88.0 | 100.0 | 97.0 |

Values are expressed as average, the benefits are epressed as percentuage (*$p < 0.05$), (**$p < 0.01$).

reported leaking urine at least once a month. On the other side the incidence of UI is highest in Caucasians (7.3/100 person-years), followed by Asians (5.7/100 person-years) and African-Americans (4.8/100 person-years).[8]

A in other studies, higher body mass index is generally considered a risk factor for incontinence, and has been confirmed in cross-sectional studies in middle aged women. Among 14,070 women aged 45 to 50 in the Women's Health Australia project, obese women (body mass index 30–40 kg/m2) had an increased risk (RR = 2.05, 95% CI 1.70–2.46) of any incontinence compared with body mass index < 20 kg/m$^2$.[5] These results are consistent with our results. In our clinical study women had an average body mass index of more than 27 kg/m$^2$. A strong correlation between body mass index and intra-abdominal pressure ($r = 0.76$, $P < 0.0001$) and intravesical pressure ($r = 0.71$, $P < 0.0001$) was found by Noblett et al.,[20] suggesting that obesity may cause a chronic state of increased pressure that stresses the pelvic floor.

Moreover, childbearing is an established incontinence risk factor.[13] Chiarelli et al.[5] observed similar odds of leaking urine among women with one childbirth (adjusted OR = 1.58, 95% CI 1.29–1.93) and women with two childbirths. The women that participated in our study had a 1.7 averaged childbirths in the grade 1 group and 2.0 in the grade 2 group. However in our clinical study we included women without childbirth (8% together). We collected information on the mode of delivery – no women with Cesarean-section.

Hannestad et al.[12] demonstrated that heavy smoking and intake of tea is related to incontinence while increasing hours of low intensity of physical activity is associated with decreased risk of incontinence. In our study non-smokers (grade 1 89% non-smoker vs. grade 2 94% non-smoker) had stress incontinence. However, a limitation of this study is that we did not obtained information about smoking history from the women participating in the study.

After menopause, women with osteoporosis are more likely to have urinary incontinence than are women with healthy bones. LaRusso[15] in the study found that therapy including pelvic floor muscle training dramatically reduces urine leakage. On the baseline in our study 24% were Kegel[4] exercise training, after 6th week the number of exercise women was increased to 42% and after 12th week there were training 47% of women. Oestrogen deficiency is an etiologic factor in the pathogenesis of several conditions.[29] Oestrogen deficiency was not definitely defined in our research; we had more than 50% of women with normal functional oestrogen.

Limited pharmacological treatment for this condition is available. In Europe only Duloxetine is available while in the United States there are not approved drugs for this disorder. Phytotherapeutic compounds are largely used in the treatment of lower urinary tract symptoms related to benign prostatic hyperplasia due to low side-effect profiles and costs, high level of acceptance by patients and a low rate of dropout. Cucurbita pepo's mechanism of action is mediated by a decrease in aromatase activity and 5-alpha-reductase.[6] The advantage of pumpkin seeds treatment arises from its tonic influence on the bladder and sphincter relaxation.[9] The pumpkin seeds yield approximately 50% oil, but the main active constituents are sterols.[1]

We identified only a few interventional studies using pumpkin seed in urinary incontinence.[32,10,19,24] A study of 39 incontinent females (aged 52–86 years) using pumpkin seed and soy isoflavone extracts (EFLA® 940) was conducted over a six-week period. The objective was to evaluate the effects on daytime and nocturnal urinary frequency and number of daily incontinent episodes. After six weeks, the nocturnal urinary frequency was improved by 39% (from 3.3 to 2.0), the daytime urinary frequency was improved by 16% (from 8.0 to 6.7) and the number of incontinent episodes was lowered by 79% (from 7.3 to 1.5).[24] In another study conducted in 50 incontinent women (aged 35–84 years) using the same pumpkin seed-soy extract supplement for six weeks, the overall improvement in all incontinent events was 67%.[32] However, there is a significant limitation in these two studies using pumpkin seed and soy isoflavone extracts, since the characteristics of participating women is missing, making hard to identify women that may respond or not to this phytotherapy.

In our study we confirmed 30% improvement in incontinence episodes frequency in women with stress urinary incontinent grade 1 and 35% improvement in grade 2 after a12-week treatment. The daytime urinary frequency significantly improved by 40% in grade 1 and 26% in grade 2. The nocturnal urinary frequency was also improved by about 64% in the grade 1 group and about 54% in the grade 2 group. In the present study we found a much better improvement in daytime incontinence frequency (difference 17%) and during the night (difference 18%) compared to using pumpkin seed and soy isoflavone extracts (EFLA® 940). However, in that study[24] a striking 79% improvement was found for incontinence episodes, nevertheless, women had a more severe baseline (7.3/day) episodes compared to our population.

To note, no adverse effects for pumpkin seeds were registered in the study by Friederich et al.[11] Only mild gastrointestinal complaints (diarrhoea, nausea, vomiting), in no more than 4% of the patients, were reported.[6] In our clinical study we found mild gastrointestinal discomfort, flatulence and headache in 10.6% of the volunteer women participating in this study while over 89% did not report side effects from these preparation. When the self-reported efficacy was analysed, 97% of women were satisfied with the CELcomplex® treatment for stress urinary incontinence. In all women with SUI grade 1 a subjective improvement was found as early as they reached the 6th week and it was maintained throughout the study. In women with SUI grade 2, the subjective improvement was 88% after 6 weeks of treatment, but all women found this therapy effective by the 12th week. This difference can be explained by the fact that grade 2 SUI is a more severe condition and may take longer to be relieved with this therapy. Some limitations should be considered. All information on frequency urinary incontinence, day time and nocturnal urinary frequency were self-reported with questionnaires. Also, this study did not have a control group.

## 5. Conclusion

This clinical study demonstrated that a 12 week treatment with a mix of Cucurbita Pepo Seed extract, Equisetum arvense and Linum usitatissimum - Flax A (CELcomplex®) is significantly effective on stress urinary incontinence (SUI) with minimum adverse events. Further studies are needed to determine the effectiveness and efficacy of this phytotherapy in other populations compared with Kegel's exercise group without CELcomplex®.

## Author declaration template

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

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