

# Extracorporeal shock wave therapy in association with bromelain and escin for the management of patients affected by chronic prostatitis/chronic pelvic pain syndrome

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**Abstract.** Extracorporeal shock wave therapy (ESWT) has been purposed for the management of chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) with encouraging results. Phytotherapeutic compounds have been used in everyday clinical practice for patients with CP/CPPS due to their anti-inflammatory properties. The present study aimed to investigate the effects of ESWT in association with the use of bromelain and escin extracts in patients with CP/CPPS. For this purpose, 95 patients with a clinical diagnosis of CP/CPPS were enrolled in the study. The patients were randomly allocated to either the ESWT plus bromelain and escin group (group A; n=48) or the ESWT only group (group B; n=47). A total of five weekly ESWT treatment sessions were administered alone or in combination with bromelain and escin. Each session consisted of 3,000 focused shock waves. Doses of 160 and 500 mg/day bromelain and escin were administered respectively for 5 weeks. The changes in urinary symptoms, pain and quality of life were considered the main outcome measures and were assessed at baseline, and at 4, 12 and 24 weeks of follow-up. Urinary symptoms, pain and quality of life were evaluated using the international prostatic symptoms score (IPSS), visual analog scale (VAS) and the National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI). After 4 weeks, the mean VAS score, mean IPSS and mean satisfaction rate score

had significantly improved in patients receiving ESWT plus bromelain and escin. After 12 weeks, the mean IPSS and mean satisfaction rate score were stable in the ESWT plus bromelain and escin group, while the mean VAS score was significantly lower when compared with the baseline values in both groups. On the whole, the present study demonstrates that in patients affected by CP/CPPS, treatment with ESWT plus bromelain and escin leads to pain resolution, and both treatments improve the IPSS, VAS and NIH-CPSI results.

## Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a clinical syndrome characterized by pain in the perineum, pelvis, suprapubic area, or external genitalia, and variable degrees of voiding and ejaculatory disturbance, without evidence of a bacterial infection. Symptoms are usually prolonged and the treatment results are unsatisfactory. CP/CPPS is classified as type 3 prostatitis following the National Institutes of Health (NIH) classification of prostatitis (1). There are several theories which are regarded as possible causes of CP/CPPS, such as pelvic floor dysfunction, stress, hormone levels and nerve dysfunctions; however, none of these theories have yet been proven (2,3). CP/CPPS remains one of the most challenging pathological condition for urologists. The diagnosis is one of exclusion and, based on significant subjective criteria, the prediction of progression is not possible, prognosis is unpredictable, and treatment is very challenging and the optimal management of category III prostatitis is not known. The impact on the quality of life of patients is thereby high (4). The current management of CPPS is based on several pharmacological and non-pharmacological approaches (5-7). Among all non-drug-based therapies, physical therapies [such as extracorporeal shock wave therapy (ESWT) and intrarectal digital massage of the pelvic floor] (8-10), psychological therapies (11) and acupuncture (12) have exhibited notable results in terms of clinical efficacy and improving the quality of life of patients. Moreover, several other

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approaches have been used and evaluated for the management of patients with CP/CPPS, such as thermobalancing, transurethral needle ablation, transcutaneous electrical nerve stimulation or sono-electromagnetic therapy, and patients treated using these approaches have exhibited a significant clinical improvement (5-7). On the other hand, phytotherapy has been used over the past years with satisfactory results as regards the relief of symptoms and quality of life (7,13,14). Several studies have been published on the roles of quercetin, bee pollen, pumpkin seed oil, eviprost or terpene mixture, with promising results (7,13,14). In particular, Cai *et al* (7) reported that flower pollen extract was able to relieve symptoms in patients affected by CP/CPPS through the reduction of interleukin (IL)-8 levels. Previous studies have demonstrated the use of escin and bromelain in the management of CP/CPPS due to its anti-inflammatory properties (15,16). The aim of the present study was to investigate the therapeutic effects of ESWT in combination with bromelain and escin in patients affected by CP/CPPS. The present study focused on changes in urinary symptoms, pain and quality of life of patients with CP/CPPS who had not undergone any other related treatments.

## Patients and methods

**Study design.** A prospective, randomized study was conducted from February, 2019 to November, 2020 on 100 male patients affected by CPPS, attending the 'Mater Domini' Hospital. The study was approved by the local ethics committee (Ethical Committee of Calabria Region, Central Section). The enrolled subjects were randomly assigned to receive either low-intensity ESWT (Li-ESWT) or Li-ESWT plus bromelain and escin. Urinary symptoms, pain and satisfaction were assessed at baseline evaluation.

**Questionnaires.** Urinary symptoms were evaluated using the international prostatic symptoms score (IPSS) (17), pain with the visual analog scale (VAS) score ranging from 0-10 (18). The NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) with three domains was used to assess the urinary symptoms, pain and the quality of life of patients (19).

**Study schedule.** A total of 95 patients with a clinical diagnosis of CP/CPPS were enrolled in the study. The patients were randomly allocated to either the ESWT plus bromelain and escin group (group A; n=48) or the ESWT only group (group B; n=47). Participants in group A received identical Li-ESWT therapy plus bromelain (a dose of 160 mg/day) and escin (a dose of 500 mg/day) for 5 weeks. Treatments were performed without anesthesia. Treatment complications were recorded. Follow-up evaluations were performed at 4 and 12 weeks after the final intervention session (Fig. 1). The Storz Duolith Li-ESWT system (Storz Medical AG) was used for the treatment sessions, which were performed once weekly for 5 consecutive weeks in both groups by the same operator. A total of 3,000 impulses were applied at each Li-ESWT session with an energy flux density of 0.25 mJ/mm<sup>2</sup> and an emission frequency of 4 Hz on the perineum area. Urinary symptoms, pain and quality of life were evaluated using the IPSS, VAS and NIH-CPSI. Each outcome was reassessed by the same operator, as reported in previous studies by the authors (20,21).

**Inclusion and exclusion criteria.** The inclusion criteria were the presence of pelvic pain symptoms for at least 3 months over the past 6 months prior to study entry in accordance with the European Association of Urology (EAU) guidelines: A score in the pain domain of the NIH-CPSI of >4; and a microbiologically negative result in the Meares-Stamey four-glass test (19,22,23). Patients with the following characteristics were excluded: Subjects <18 and >50 years of age; patients affected by major concomitant diseases with known anatomical abnormalities of the urinary tract or with evidence of other urological diseases; patients with residual urine volume >50 ml resulting from bladder outlet obstruction; subjects with a reported allergy to pollen extract; patients who had recently (<4 weeks) undergone oral or parenteral treatment, or who were currently using prophylactic antibiotic drugs; all patients positive to tests for *Chlamydia trachomatis*, *Ureaplasma urealyticum*, *Neisseria gonorrhoeae*, herpes viruses (HSV 1/2) and human papillomavirus (HPV) (22).

**Ethical considerations.** The present study was approved by the University of Catanzaro Institutional Review Board (no. 48 of 22th February 2019). The study was conducted in line with Good Clinical Practice guidelines, in compliance with the ethical principles published in the latest version of the Declaration of Helsinki (24). Written informed consents were obtained from all patients prior to treatment.

**Statistical analysis.** The homogeneity of the groups at baseline was assessed using Mann-Whitney U test for continuous variables. Multiple comparisons between the two groups at the baseline and each follow-up evaluation time point was performed using the Kruskal-Wallis test. Post hoc analysis was performed using the Dunn's multiple comparison test. General characteristics of the study participants were expressed with descriptive statistics (means, standard deviations or ranges). The calculation of the sample size needed for enrollment was based on the expected questionnaire results (improvement of quality of life) in line with published results from other studies (14,20,21). The required sample size was calculated under the following conditions: Difference between the groups, 35% of patients who reach a reduction in 15% of the NIH-CPSI total score;  $\alpha$  error level, 0.05 two-sided; statistical power, 80%; and anticipated effect size, Cohen's d=0.5. The calculations yielded at least 44 individuals per group. A value of P<0.05 was considered to indicate a statistically significant difference. All reported P-values were two-sided. Statistical analyses were performed using SPSS software, version 11.0 (SPSS, Inc.) for Apple-Macintosh.

## Results

At the end of the follow-up period, 95 patients were available for follow-up examinations and analyzed: 48 patients in group A (Li-ESWT in association with bromelain and escin) and 47 in group B (Li-ESWT only). Differences in pre-treatment characteristics between the Li-ESWT and control groups were not statistically significant. No major complications were observed in patients receiving both treatments, and all patients tolerated the treatments well. None of the patients required the administration of analgesics during treatment. The patient clinical characteristics at baseline are presented in Table I.

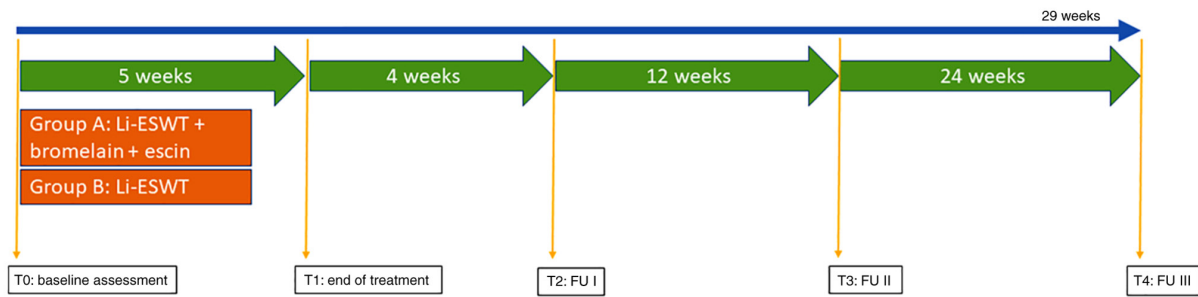


Figure 1. Schematic diagram of the study design and schedule.

Table I. Baseline assessment.

| Parameter        | Group A<br>(n=48) | Group B<br>(n=47) | P-value |
|------------------|-------------------|-------------------|---------|
| Age (years)      | 32 (5)            | 31 (6)            | 0.89    |
| IPSS             | 15 (4)            | 15 (4)            | 0.99    |
| VAS              | 5 (2)             | 6 (3)             | 0.78    |
| NIH-CP/CPSI      |                   |                   |         |
| Pain domain      | 13 (2)            | 13 (2)            | 0.99    |
| Urinary symptoms | 6 (2)             | 6 (2)             | 0.99    |
| Quality of life  | 9 (3)             | 10 (4)            | 0.84    |

The table shows the baseline characteristics of all enrolled patients. IPSS, international prostatic symptoms score; VAS, visual analogue scale; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index. All data are presented as the median and Interquartile range (IQR). The Mann-Whitney U test was used for the analysis.

**Follow-up assessment at 4 weeks.** At 4 weeks follow-up, out of the patients assigned to the group treated with Li-ESWT alone, 3 (6%) patients reported pain disappearance, 25 (53%) reported pain reduction, 17 (36%) reported pain stability and 5 (10%) reported pain worsening. In the Li-ESWT plus bromelain and escin group, 4 (8%) reported pain disappearance and 29 (60%) reported pain reduction; pain remained stable in 14 patients (29%) and worsened in 3 patients (6%). The median IPSS scores were significantly lower in both groups when compared with the baseline values [15; (IQR 4) and 15 (IQR 4) vs. 10 (IQR 5) and 10 (IQR 6) for group A and B, respectively;  $P<0.001$ ;  $P<0.001$ ] (Table II). No significant differences emerged in the scores between the two different groups. The same trend was observed for the median VAS score (5; IQR 2 and 6; IQR 3 vs. 4; IQR 2 and 4; IQR 2 for groups A and B, respectively;  $P<0.001$ ;  $P<0.001$ ). The median scores of the three domains of NIH-CPSI exhibited significant differences compared to baseline values [13 (IQR 2) and 13 (IQR 2) vs. 8 (IQR 4) and 7 (IQR 4) for pain domain ( $P<0.001$ ;  $P<0.001$ ); 6 (IQR 2) and 6 (IQR 2) vs. 4 (IQR 4) and 4 (IQR 3) for urinary symptoms domain ( $P<0.001$ ;  $P<0.001$ ); 9 (IQR 3) and 10 (IQR 4) vs. 7 (IQR 4) and 7 (IQR 5) for quality-of-life domain ( $P<0.001$ ;  $P<0.001$ ) in group A and B, respectively], although no differences were found between the two groups at 4 weeks of follow-up (Table II). All follow-up findings at 4 weeks are presented in Table III.

**Follow-up assessment at 12 weeks.** At 12 weeks of follow-up in both groups, the median IPSS scores were lower, although not significantly, when compared with the follow-up values at 4 weeks [10 (IQR 5) and 10 (IQR 6) vs. 10 (IQR 5) and 9 (IQR 5) for groups A and B, respectively;  $P=0.99$ ;  $P=0.08$ ]. No significant differences emerged in the scores between the two different groups. The median VAS score was not significantly lower compared to the 4 weeks of follow-up for group B [4 (IQR 2) vs. 4 (IQR 3);  $P=0.98$ ]. Conversely the median score was significantly lower in group A when compared to the first follow-up [4 (IQR 2) vs. 1 (IQR 2)  $P<0.001$ ] and to group B [4 (IQR 3) vs. 1 (IQR 2);  $P<0.001$ ] (Table II). As regards the median scores of the three domains of NIH-CPSI, the pain and quality of life domains exhibited significant differences between groups A and B [8 (IQR 4) vs. 4 (IQR 2) 7 (IQR 3) vs. 4 (IQR 2)  $P<0.001$ ;  $P<0.001$ ]. At 12 weeks follow-up, out of the patients assigned to the ESWT plus bromelain and escin group, 2 (4.16%) reported pain disappearance and 25 (52.0%) reported pain reduction; pain remained stable in 14 patients (29.7%) and worsened in 6 patients (12.5%). In the ESWT-alone group, 2 (4.25%) patients reported pain disappearance, 22 (46.8%) reported pain reduction, 20 (42.5%) reported pain stability, and 4 (8.5%) reported pain worsening. All follow-up findings at 12 weeks are displayed in Table IV.

**Follow-up assessment at 24 weeks.** At 24 weeks follow-up in both groups, the median IPSS scores were similar compared with the 4- and 12-week follow-up values, without any significant difference between the two groups [11 (IQR 5) vs. 11 (IQR 5) for A and B group respectively;  $P=0.99$ ]. The median VAS score was significantly lower for group A than group B [1 (IQR 2) vs. 4 (IQR 2)  $P<0.001$ ]. As regards the median scores of the three domains of NIH-CPSI, the pain and quality of life domains exhibited significant differences between groups A and B [8 (IQR 2) vs. 5 (IQR 2);  $P<0.001$ ; 7 (IQR 2) vs. 4 (IQR 2)  $P<0.001$ ]. At 24 weeks of follow-up, out of the patients assigned to the Li-ESWT plus bromelain and escin group, 2 (4.16%) reported pain disappearance and 19 (39.58%) reported stable pain reduction; pain remained stable in 18 patients (37.5%) and worsened in 8 patients (16.6%). In the Li-ESWT -alone group, 2 (4.25%) patients reported pain disappearance, 15 (31.91%) reported stable pain reduction, 23 (48.93%) reported pain stability, and 8 (17.02%) reported pain worsening. The mean IPSS score was lower when compared with baseline values in the Li-ESWT plus bromelain and escin group, but not significantly, while no statistically significant differences were found in the

Table II. Comparison between baseline and follow-up data.

| Parameter        | Group A (n=48) |         |          |          | P-value<br>(vs. baseline) |
|------------------|----------------|---------|----------|----------|---------------------------|
|                  | Baseline       | 4 weeks | 12 weeks | 24 weeks |                           |
| IPSS             | 15 (4)         | 10 (5)  | 10 (5)   | 11 (5)   | <0.001 (all)              |
| P-value          |                | <0.001  | 0.99     | 0.33     |                           |
| VAS              | 5 (2)          | 4 (2)   | 1 (2)    | 1 (1)    | <0.001 (all)              |
| P-value          |                | <0.001  | <0.001   | 0.99     |                           |
| NIH-CP/CPSI      |                |         |          |          |                           |
| Pain domain      | 13 (2)         | 8 (4)   | 8 (4)    | 8 (2)    | <0.001 (all)              |
| P-value          |                | <0.001  | 0.99     | 0.87     |                           |
| Urinary symptoms | 6 (2)          | 4 (4)   | 4 (3)    | 4 (2)    | <0.001 (all)              |
| P-value          |                | <0.001  | 0.88     | 0.76     |                           |
| Quality of life  | 9 (3)          | 7 (4)   | 4 (2)    | 5 (2)    | <0.001 (all)              |
| P-value          |                | <0.001  | <0.001   | 0.67     |                           |
| Parameter        | Group B (n=47) |         |          |          | P-value<br>(vs. baseline) |
|                  | Baseline       | 4 weeks | 12 weeks | 24 weeks |                           |
| IPSS             | 15 (4)         | 10 (6)  | 9 (5)    | 11 (4)   | <0.001 (all)              |
| P-value          |                | <0.001  | 0.08     | 0.33     |                           |
| VAS              | 6 (3)          | 4 (2)   | 4 (3)    | 4 (2)    | <0.001 (all)              |
| P-value          |                | <0.001  | 0.98     | 0.98     |                           |
| NIH-CP/CPSI      |                |         |          |          |                           |
| Pain domain      | 13 (2)         | 7 (4)   | 4 (2)    | 5 (2)    | <0.001 (all)              |
| P-value          |                | <0.001  | 0.98     | 0.65     |                           |
| Urinary symptoms | 6 (2)          | 4 (3)   | 4 (2)    | 4 (2)    | <0.001 (all)              |
| P-value          |                | <0.001  | 0.98     | 0.99     |                           |
| Quality of life  | 10 (4)         | 7 (5)   | 7 (3)    | 7 (2)    | <0.001 (all)              |
| P-value          |                | <0.001  | 0.98     | 0.98     |                           |

The table shows the follow-up findings in comparison with the baseline and the other follow-up evaluations. Comparisons were made between 4 weeks and baseline, 12 weeks and 4 weeks, and between 24 weeks to 12 weeks. IPSS, international prostatic symptoms score; VAS, visual analogue scale; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index. All data are presented as the median and Interquartile range (IQR). The Kruskal-Wallis test and Dunn's multiple comparison test were used for statistical analysis.

Li-ESWT group (Table II). All follow-up findings at 24 weeks are presented in Table V.

**Adverse effects.** No clinically significant adverse effects were reported. Two patients reported mild pain (VAS 1) during the procedure in the ESWT application area. All results of safety profile are presented in Table VI.

## Discussion

The present study demonstrated that the use of bromelain plus escin improved the clinical efficacy of Li-ESWT in patients affected by CP/CPPS, by ameliorating urinary symptoms, pain and the quality of life.

At the present time, to the best of our knowledge, there are no studies available that used both Li-ESWT and phytotherapy and that have compared the two treatments. It was

hypothesized that the higher clinically significant improvement observed in the quality of life of patients treated with Li-ESWT and phytotherapy was due to the anti-inflammatory effects of bromelain and escin which were enhanced by Li-ESWT. Several researchers, in this sense, have reported a significant anti-inflammatory effects of bromelain and escin in several aspects of clinical practice (15,16,25). The efficacy of Li-ESWT treatment in patients affected by CP/CPPS has been demonstrated in several clinical studies, reporting a significant relief in pelvic pain and voiding symptoms in patients with CPPS (26-28). Recently, Kim *et al* (29) in a randomized control trial, demonstrated that Li-ESWT improved the NIH-CPSI score, pain and the quality of life of patients with CPPS IIIb. Moreover, they concluded that Li-ESWT could be an effective alternative treatment modality for CPPS IIIb (29). The clinical efficacy of Li-ESWT in patients with CP/CPPS is probably due some hypothesized mechanism, such as nociceptor

Table III. Assessment at 4 weeks of follow-up.

| Parameter        | Group A<br>(n=48) | Group B<br>(n=47) | P-value |
|------------------|-------------------|-------------------|---------|
| IPSS             | 10 (5)            | 10 (6)            | 0.99    |
| VAS              | 4 (2)             | 4 (2)             | 0.99    |
| NIH-CP/CPSI      |                   |                   |         |
| Pain domain      | 8 (4)             | 7 (4)             | 0.86    |
| Urinary symptoms | 4 (4)             | 4 (3)             | 0.99    |
| Quality of life  | 7 (4)             | 7 (5)             | 0.99    |

The table shows the follow-up findings at 4 weeks. IPSS, international prostatic symptoms score; VAS, visual analogue scale; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index. All data are presented as the median and Interquartile range (IQR). The Mann-Whitney U test was used for the analysis.

Table IV. Assessment at 12 weeks of follow-up.

| Parameter        | Group A<br>(n=48) | Group B<br>(n=47) | P-value |
|------------------|-------------------|-------------------|---------|
| IPSS             | 10 (5)            | 9 (5)             | 0.78    |
| VAS              | 4 (3)             | 1 (2)             | 0.001   |
| NIH-CP/CPSI      |                   |                   |         |
| Pain domain      | 8 (4)             | 4 (2)             | 0.001   |
| Urinary symptoms | 4 (3)             | 4 (2)             | 0.99    |
| Quality of life  | 7 (3)             | 4 (2)             | 0.001   |

The table shows the follow-up findings at 12 weeks. IPSS, international prostatic symptoms score; VAS, visual analogue scale; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index. All data are presented as the median and Interquartile range (IQR). The Mann-Whitney U test was used for the analysis.

hyperstimulation, nitric oxide synthesis induction, passive muscle tone decreasing, the interruption of nerve impulses and an increase in local microvascularization. Moreover, Jeon *et al* (30) highlighted, by using an animal model, that Li-ESWT reduced COX-2 levels by inhibiting the TLR3-NF- $\kappa$ B pathway. Furthermore, in their study, the TRAF2 regulator in ERK1/2 inhibition significantly decreased inflammation (30). The authors also demonstrated that these signaling pathways facilitated inflammation with different levels of the expression of IL-1 $\beta$ , IL-6 and other inflammatory molecular markers via different stimulation models (30). From a clinical perspective, recently, Li and Man (31) reported the results of a systematic review and meta-analysis, including six studies involving 317 male patients exhibiting significant clinical improvements in terms of total NIH-CPSI scores, quality of life, pain scores and urinary symptom scores in the Li-ESWT group compared to the control group at 12 weeks following treatment. The present study considered the efficacy of the no-drug approach with a phytotherapy compound. The hypothesis to combine two approaches, a no-drug and a drug approach was based on

Table V. Assessment at 24 weeks of follow-up.

| Parameter        | Group A<br>(n=48) | Group B<br>(n=47) | P-value |
|------------------|-------------------|-------------------|---------|
| IPSS             | 11 (5)            | 11 (4)            | 0.99    |
| VAS              | 4 (2)             | 1 (1)             | 0.001   |
| NIH-CP/CPSI      |                   |                   |         |
| Pain domain      | 8 (2)             | 5 (2)             | 0.001   |
| Urinary symptoms | 4 (2)             | 4 (2)             | 0.99    |
| Quality of life  | 7 (2)             | 4 (2)             | 0.001   |

The table shows the follow-up findings at 24 weeks. IPSS, international prostatic symptoms score; VAS, visual analogue scale; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index. All data are presented as the median and Interquartile range (IQR). The Mann-Whitney U test was used for the analysis.

Table VI. Safety profile.

| Parameter                 | Group A<br>(n=48) | Group B<br>(n=47) | P-value |
|---------------------------|-------------------|-------------------|---------|
| Discomfort                |                   |                   |         |
| VAS (0-2)                 | 1 (2)             | 1 (2)             | 0.99    |
| Gastrointestinal symptoms |                   |                   |         |
| Mild                      | 1                 | 0                 | 0.87    |

The table shows the safety profile.

the necessity to act in several pathophysiological pathways in patients with CP/CPPS, as suggested by Magistro *et al* (32). The association between Li-ESWT and bromelain and escin was able to improve the clinical efficacy due to the anti-inflammatory effects of bromelain and escin. It has been demonstrated that bromelain is able to reduce the levels of certain inflammatory mediators, such as NF- $\kappa$ B, IL-1 $\beta$ , IL-6, TNF- $\alpha$ , PGE2 and nitrate concentrations (33). In the same manner, escin, a natural mixture of triterpenoid saponins has been demonstrated to exert anti-edematous and anti-inflammatory effects (16,34). In this sense, the efficacy of the association between Li-ESWT and phytotherapy is increased by the effects of the association to inhibit several inflammatory pathways involved in the complex pathogenesis of the CP/CPPS. Due to these notable results in males, this approach may be also evaluated for managing pelvic pain syndrome in female patients in the future.

The present study has certain limitations. Firstly, the lack of a placebo should be considered. This aspect was considered in the analysis and interpretation of the results. The placebo effect in phytotherapy research ranges from 20 to 30%, as highlighted by Capasso *et al* (35). On the basis of this consideration, a clinically significant difference between the two groups was considered when >30%. Finally, the short follow-up period should be considered among the study limitations.

In conclusion, the present study demonstrates that in patients with CP/CPPS, Li-ESWT plus bromelain and escin leads to pain resolution and both treatments ameliorate

IPSS, VAS and NIH-CP/CPSI. However, further studies are warranted to confirm these results.

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## Availability of data and materials

The datasets generated and/or analyzed during the current study are not publicly available due to Italian law on privacy but are available from the corresponding author on reasonable request.

## Authors' contributions

LDL, ADG, LC and GLC collected and analyzed the data. AP, CDA, TC, LG and MC were involved in the study conception, design, analysis of data and in the writing of the manuscript. LDL and AP confirm the authenticity of all the raw data. All authors have read and approved the final manuscript.

## Ethics approval and consent to participate

The present study was approved by the University of Catanzaro Institutional Review Board (no. 48 of 22th February 2019). The study was conducted in line with Good Clinical Practice guidelines, in compliance with the ethical principles published in the latest version of the Declaration of Helsinki. Written informed consents were obtained from all patients prior to treatment.

## Patient consent for publication

Not applicable.

## Competing interests

The authors declare that they have no competing interests.

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