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Oral Immunoglobulins from Bovine Colostrum and Anti-Inflammatory Extracts in Patients with Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Prospective Study

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Abstract

Background: Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a bothersome condition characterized by pelvic pain and lower urinary tract symptoms (LUTS). Phytotherapy can be used to treat this challenging condition. The aim of this study was to investigate the role of an oral combination of bovine colostrum, *Serenoa repens* extract and other anti-inflammatory elements in the treatment of CP/CPPS patients. **Methods**: Our study was a prospective, observational, single-arm study that enrolled patients > 18 years with a history consistent with CP/CPPS, a Chronic Prostatitis Symptom Index (CPSI) pain domain score ≥ 5 and a Meares–Stamey microbiological test negative for bacterial infection. Pelvic or genital pain was measured via the Numeric Pain Rating Scale (NPRS) and validated questionnaires. All patients were treated with an oral combination of colostrum, *Serenoa repens* extract and other anti-inflammatory elements for 6 months. Follow-up visits were scheduled at 3 and 6 months. Pre- and post-treatment variables were compared by means of the Wilcoxon signed-rank nonparametric test. **Results**: We included 42 patients in our analysis. The median (Inter-Quartile Range, IQR) age was 42 (28–51) years. Compared with baseline, after 3 months we observed a significant reduction in pain: total CPSI score of 16 (12–21) vs. 22 (17–26), $p < 0.001$, −6 points (−27.3%); CPSI score of "pain" domain 7 (5–9) vs. 8 (7–11), $p < 0.001$, −1 point (−12.5%). Moreover, quality of life improved: CPSI "quality of life" domain 6 (4–9) vs. 8 (7–10), $p < 0.001$. After 6 months, a significant reduction in pain was maintained: total CPSI score 19 (10–23), $p < 0.001$, −3 points (−13.65%); and CPSI "pain" domain 7 (4–9), $p < 0.001$, −1 point (−12.5%). After 6 months, a mild reduction in urinary symptoms was also reported. During the observation period, five patients discontinued treatment, two of them because of gastrointestinal intolerance. **Conclusions**: The daily oral administration of bovine colostrum, *Serenoa repens* and other anti-inflammatory elements showed a potential in improving pain and other urinary symptoms and was generally well tolerated by patients affected by CP/CPPS.

Keywords: chronic prostatitis; chronic pelvic pain syndrome; bovine colostrum; *Serenoa repens*; LUTS (lower urinary tract symptoms); pain

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1. Introduction

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), also named as category III prostatitis by the National Institute of Health [1], can be defined as a bothersome medical condition characterized by pain localized to the pelvic and genital areas. CP/CPPS patients often report urinary symptoms and psychological distress, resulting in a significant reduction in their quality of life. CP/CPPS is a frequent condition, as the average prevalence of prostatitis ranged from 2.2% to 12.2% in the adult male population [2]. Among urologists, CP/CPPS is considered a difficult-to-treat disease [2,3]. CP/CPPS treatment has involved the use of empirical antibiotics for a long time [4], even if reports of long-term lack of efficacy were more and more widespread in international literature [5]. More recently, the development of an antibiotic stewardship and promising emerging therapeutic agents shifted the attention toward phytotherapy, which progressively gained value as an alternative in the context of a multimodal therapeutic approach. As a monotherapy or a combination of two or more compounds, phytotherapy consistently demonstrated efficacy in mitigating patients' pain and discomfort while improving their quality of life [6,7].

Among the wide range of compounds currently available for the treatment of CP/CPPS symptoms, colostrum represents a novel treatment [6]. Preclinical evidence has demonstrated its efficacy against chronic inflammation due to its components: lactoferrin binds iron, thereby limiting bacterial growth, and exerts direct anti-inflammatory effects, including inhibition of NF-κB activation and reduction in pro-inflammatory cytokine production. In addition, growth factors such as IGF-1, TGF-β, and EGF promote tissue repair following stress-induced damage. Among these, TGF-β also displays a direct immunomodulatory effect by attenuating excessive inflammatory responses. Finally, bovine colostrum is potentially responsible for immunomodulation because of its high content of immunoglobulins that can be transferred by ingestion [8,9]. Previous in vivo tests have shown promising results in urological and gynecological contexts [10,11]. Owing to its marked anti-inflammatory properties, colostrum is considered a candidate for the treatment of chronic prostatitis, but its efficacy still needs to be tested in a real-life clinical scenario. *Serenoa repens* (saw palmetto) extract is another well-known and commonly prescribed phytotherapy agent that has been found to be effective for the treatment of benign prostatic hyperplasia (BPH) symptoms [12]. *Serenoa repens* extract was found effective in targeting chronic prostatic inflammation, specifically when related to the onset and progression of BPH, while its beneficial effects in chronic prostatitis patients were more controversial. However, a beneficial effect was reported in several literature reports [13–15]. PROSTYM® (Rubio Nutraceuticals, Milan, Italy) is an oral formulation that combines bovine colostrum and *Serenoa repens* in a single capsule and is currently available for the pharmacological treatment of prostate-related inflammatory symptoms and BPH.

The aim of this study was to prospectively evaluate the efficacy of PROSTYM® for the treatment of CP/CPPS symptoms, including patient-reported pain, urinary symptoms, and quality of life. The tolerability of this compound after prolonged use was also assessed.

2. Materials and Methods

This study was a monocentric, prospective, single-arm, observational trial (A.O.U. Città della Salute e della Scienza, Molinette Hospital, University of Turin, Turin, Italy). The study was conducted according to the Helsinki declaration and approved by our local ethics committee (Comitato Etico Interaziendale, CET, AOU Città della Salute e della Scienza, n. 00054/2019). All patients signed a specific informed consent form.

From March 2020 to December 2022, all patients referred to our urology unit with symptoms suspicious for CP/CPPS underwent a thorough clinical evaluation, including digital rectal examination, an abdominal ultrasound to measure prostate volume, and a mi-

crobiological Meares and Stamey test [16]. All patients completed validated questionnaires, including the International Prostate Symptom Score (IPSS), which is a 7-item questionnaire widely used to evaluate the severity of lower urinary tract symptoms. It includes questions addressing both storage and voiding symptoms, each scored from 0 to 5, yielding a total score range of 0 to 35. Symptom severity is commonly categorized as mild (0–7), moderate (8–19), or severe (20–35) [17,18]; the Chronic Prostatitis Symptom Index (CPSI) is a 13-item, disease-specific questionnaire designed to assess symptom severity and impact in men with chronic prostatitis/chronic pelvic pain syndrome. It comprises three domains. The first domain is pain (items 1–4; score range 0–21). Notably, item 1 is further subdivided into 1a, 1b, 1c, and 1d questions; item 2 is further subdivided into 2a and 2b questions. The second domain is urinary symptoms (items 5–6; score range 0–10). The third domain is quality of life impact (items 7–9; score range 0–12). The total score ranges from 0 to 43, with higher scores indicating mild (0–14), moderate (15–29) and severe (30–43) symptoms and worse quality of life [19]. Notably, a CPSI "pain" domain score ≥ 8 defined a significant level of pain [20]. The International Index of Erectile Function (IIEF5) is a shortened, 5-item version of the International Index of Erectile Function, designed to assess erectile function over the preceding months. Each item is scored from 1 to 5, resulting in a total score range of 5 to 25. Higher scores indicate better erectile function [21]. Finally, we submitted to the patients the Numeric Pain Rate Scale, which ranges from 0 (absence of pain) to 10 (the worst pain ever experienced), with a score of 4–6 defining a moderate level of pain. Baseline and post-treatment prostate-specific antigen (PSA) serum levels were also measured. As a prostate-specific, but not disease-specific marker, PSA can be measured in chronic prostatitis patients to evaluate the anti-inflammatory response to treatment and help discriminate benign conditions from potentially neoplastic ones [22]. We analyzed pre- and post-treatment PSA values as a potential marker of the anti-inflammatory activity of the study compound.

2.1. Inclusion Criteria

In our study, we included adult male patients (aged >18 years) who were clinically affected by CP/CPPS with symptoms that persisted for $\geq$6 months. Only patients with a CPSI pain domain score $\geq$ 5 points and a negative Meares and Stamey test score were enrolled. We excluded patients with prevalent BPH symptoms (CPSI pain domain < 5), acute prostatitis, chronic bacterial prostatitis (positive Meares and Stamey test), prostate or bladder cancer, urethral stenosis or neurological bladder. To avoid the confounding effect of other treatments, all patients did not receive any other drug or supplement specific to chronic prostatitis in the previous 30 days. Finally, patients with abnormal PSA or PSA values requiring further investigations ($\geq$3 ng/mL) were excluded [23]. The recruitment process and the distribution of the study population, including exclusions and the final analyzed cohort, are summarized in the study flow chart (Figure 1).

2.2. Treatment

PROSTYM® is an oral combination of colostrum and *Serenoa repens*, with a recommended daily dose of 1 capsule per day. All patients were administered PROSTYM®, one capsule, daily for 6 months.

The composition of PROSTYM® (per capsule) includes bovine colostrum (30 mg), Serenoa extracts (320 mg), glutathione (30 mg), N-acetyl cysteine (20 mg), Ribes nigrum extracts (50 mg), willow extracts (50 mg), zinc (5 mg), selenium (27.5 µg), and vitamin E (6 mg).

The compound was provided to all patients without any charge, as per the ethical committee's instructions. PROSTYM® capsules were dispensed in two tranches: at baseline, after providing informed consent, and after the first follow-up at 3 months.

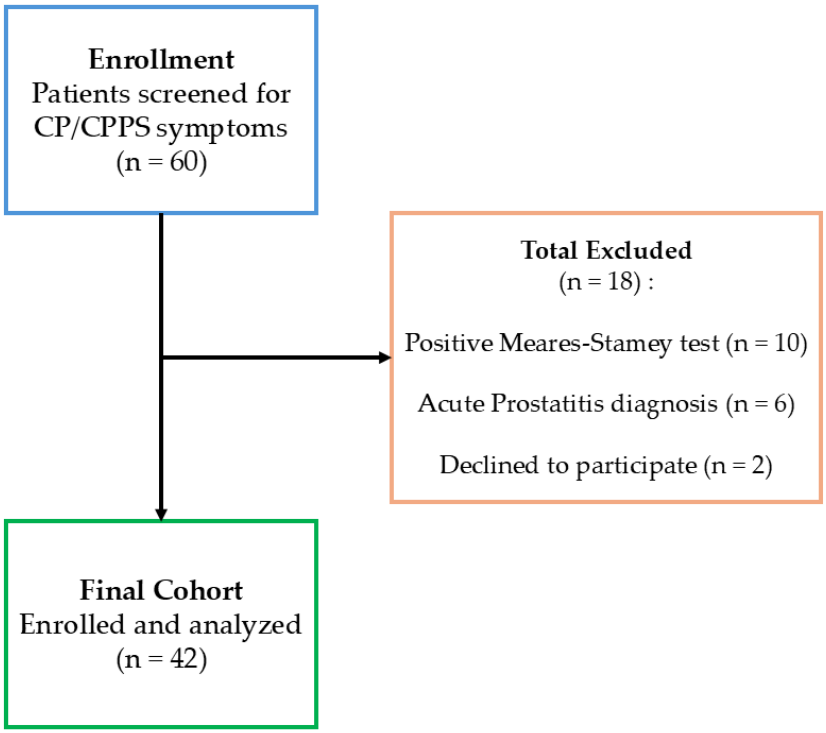


Figure 1. Study Flow Diagram. This chart illustrates the enrollment process of the study population. From the 60 consecutive patients screened, 18 were excluded based on specific clinical and microbiological criteria (positive Meares–Stamey tests, acute prostatitis, or refusal to participate), resulting in a final analyzed cohort of 42 patients.

2.3. Follow-Up

Follow-up visits were scheduled at 3 and 6 months. At each visit, the IPSS, CPSI and IIEF5 were administered. To provide questionnaires to patients, we chose the technique of self-administration followed by a quality check and doubt-solving by medical personnel.

Any patient-reported issues about the safety or tolerability of the product were registered. Whenever a significant adverse event was reported, the pharmacological treatment was immediately stopped. If patients were not able to undergo in-person follow-up visits, they were contacted by phone. If no contact was possible, even by phone, patients were deemed lost to follow-up.

In the context of this follow-up schedule, we were also able to verify patient adherence to the therapy.

2.4. Statistical Analysis

Continuous variables were reported as medians and interquartile ranges (IQRs). Categorical variables were reported as numbers and percentages. We defined the subsequent variables: age and prostate volume. Moreover, questionnaire scores were also considered as continuous variables (CPSI scores, IPSS and IPSS QoL scores, IIEF5 scores, NRS scores). On the contrary, all variables admitting a binary (yes/no) response were considered as categorical. In our analysis, the status of the Meares and Stamey test (positive/negative) and cigarette smoke (yes/no) were considered as categorical. Pre- and post-treatment variables were compared by means of the Wilcoxon signed-rank nonparametric test. Statistical

significance was considered when a p-value < 0.05 was obtained. The software used for analysis was Stata® version 16.0 (StataCorp LLC, College Station, TX, USA).

A power calculation was performed based on the primary outcome. Given an alpha error = 0.05, a 1-beta error = 0.80, and an estimated effect size of 0.4, a sample size of 41 patients was estimated for the study to be adequately powered. No AI software was used by the authors to create, modify or edit this manuscript.

3. Results

Overall, 60 consecutive patients were screened for this study. As shown in Figure 1, 18 patients were excluded: 10 due to positive Meares–Stamey tests, 6 diagnosed with acute prostatitis, and 2 who declined to participate. Consequently, 42 patients were enrolled in the PROSTYM® study cohort (Figure 1).

The median age of the included patients was 42 (28–51) years. All included patients were negative according to the Meares–Stamey test. Table 1 shows the baseline features of the enrolled patients, including the median questionnaire scores. Notably, the included patients had significant levels of prostatitis symptoms and pain at baseline: the CPSI median total score was 22 (17–26), indicating moderate levels of symptoms [19], and the CPSI median "pain" domain score was 8 (7–11), indicating a significant level of pain [20].

Table 1. Baseline features of included patients.

Age, Years, Median (IQR)	**42 (28–51)**
Negative Meares and Stamey test, n (%)	42 (100)
Prostate volume, cc, median (IQR)	70 (50–98.5)
Cigarette smoke	
yes	7 (16.67)
no	35 (83.33)
IPSS, median (IQR)	10.5 (8–21)
IPSS quality of life domain, median (IQR)	4 (2–4)
CPSI score, median (IQR)	22 (17–26)
CPSI pain domain, median (IQR)	8 (7–11)
CPSI micturition domain, median (IQR)	4 (2–6)
CPSI quality of life domain, median (IQR)	8 (7–10)
IIEF5 score, median (IQR)	19.5 (14–23)
NPRS score, median (IQR)	5 (3–6)

IQR: Interquartile range; IPSS: International Prostate Symptom Score; IIEF: International Index of Erectile Function; CPSI: Chronic Prostatitis Symptom Index; NPRS: Numeric Pain Rating Scale.

At 3 months, daily treatment with PROSTYM® had been administered to 37 out of 42 patients. In two patients, treatment was discontinued due to gastrointestinal intolerance, whereas three patients were lost to follow-up. Among these three patients, one abandoned the study due to the concomitant diagnosis of a neurological disease, while the other two never responded to follow-up calls and visits. The questionnaire scores revealed a significant reduction in pain compared with the baseline scores: the CPSI total score was 16 (12–21), $p < 0.001$, −6 points (−27.3%), and the CPSI pain domain score was 7 (5–9), $p < 0.001$, −1 point (−12.5%). Conversely, we observed a nonsignificant modification of nonpainful urinary symptoms and erectile function: IPSS 12 (6–16), $p = 0.539$, +1.5 points (+12.5%); CPSI "micturition" domain 3 (2–5), $p = 0.116$, −1 point (−25%); and IIEF5 20 (14–23), $p = 0.664$, +0.5 points (+2.5%). Together with a reduction in pain, we

observed an improvement in patient-reported quality of life, with a CPSI "quality of life" domain score of 6 (4–9), $p = 0.001$, −2 points (−25%) [Table 2].

Table 2. Three and 6-month follow-up after daily treatment with PROSTYM®.

	Baseline	3 Months	6 Months	*p*-Value
IPSS, median (IQR)	10.5 (8–21)	12 (6–16)	9 (4–18)	0.056 [a] 0.446 [b] 0.539 [c]
IPSS quality of life	4 (2–4)	4 (3–5)	3 (2–5)	0.316 [a] 0.073 [b] 0.652 [c]
CPSI (total)	22 (17–26)	16 (12–21)	19 (10–23)	**<0.001** [a] 1.000 [b] **<0.001** [c]
CPSI (pain)	8 (7–11)	7 (5–9)	7 (4–9)	**<0.001** [a] 0.291 [b] **<0.001** [c]
CPSI (micturition)	4 (2–6)	3 (2–5)	3 (2–5)	**0.017** [a] 0.385 [b] 0.116 [c]
CPSI (quality of life)	8 (7–10)	6 (4–9)	6 (3–9)	**0.003** [a] 0.931 [b] **0.001** [c]
IIEF5	19.5 (14–23)	20 (14–23)	21 (16–23)	0.133 [a] 0.654 [b] 0.664 [c]
NPRS	5 (3–6)	5 (2–5)	5 (3–6)	**0.049** [a] 0.431 [b] **0.014** [c]

[a] Six-month results compared to baseline; [b] 6-month versus 3-month results; [c] 3-month results compared to baseline. Statistics: Wilcoxon signed-rank test. IPSS: International Prostate Symptom Score; IIEF: International Index of Erectile Function; CPSI: Chronic Prostatitis Symptom Index; NPRS: Numeric Pain Rating Scale.

At 6 months, no additional treatment discontinuations were registered. Moreover, we did not report further adverse events while the improvement in symptoms was maintained, compared to baseline. The degree of pain was significantly lower than that at baseline: the CPSI total score was 19 (10–23), $p < 0.001$, −3 points (−13.65%); the CPSI pain domain score was 7 (4–9), $p < 0.001$, −1 point (−12.5%). The pain scores at 6 months did not significantly differ from those reported after 3 months. Urinary symptoms globally appeared slightly improved compared to baseline and 3-month evaluations. Specifically, we observed a decrease in the CPSI micturition domain [3 (2–5) points, −1 point, $p = 0.017$], while the IPSS values did not show statistically significant differences despite a median reduction of −1.5 points, compared to baseline. Finally, patient-reported quality of life significantly improved at the end of the therapy period: the final CPSI "quality of life" domain score was 6 (3–9), $p = 0.003$ [Table 2].

Baseline median PSA value was 1.3 (1–2.2) ng/mL. Median PSA value after 6 months was 2.55 (1.25–3.65) ng/mL, $p = 0.317$ (Figure 2).

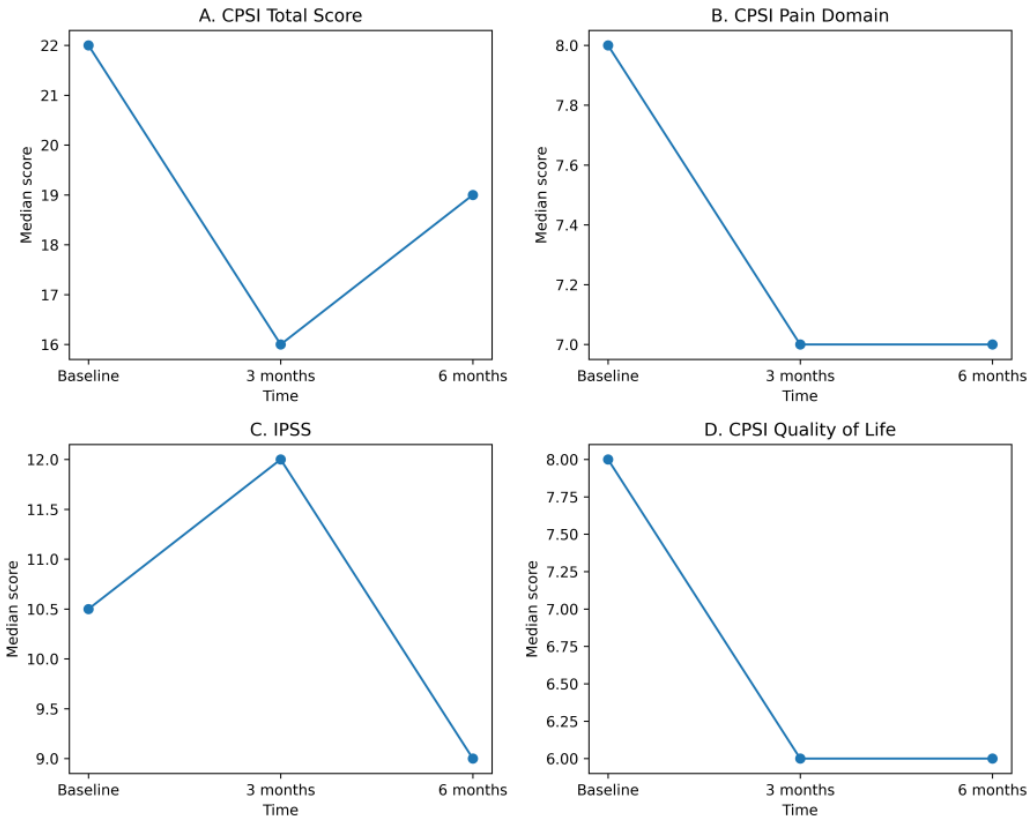


Figure 2. Longitudinal changes in symptom scores. (**A**) CPSI total score over time: clear reduction at 3 months, with partial maintenance at 6 months; (**B**) CPSI pain domain score over time: rapid reduction by 3 months, maintained at 6 months; (**C**) IPSS over time: slight worsening at 3 months, followed by improvement at 6 months; (**D**) CPSI quality-of-life domain score over time: marked improvement at 3 months, maintained through 6 months.

4. Discussion

Nonbacterial chronic prostatitis (CP/CPPS) is considered a difficult-to-treat condition by most urologists. An accurate diagnosis and timely and tailored treatment are key for better control of symptoms while avoiding empirical antibiotic therapies when negative Meares and Stamey tests are obtained [24]. The tolerability and compliance of prolonged pharmacological therapies are other issues. In many cases, even when effective, active compounds cannot be proposed for long-term administration. The perfect example is represented by nonsteroidal anti-inflammatory drugs (NSAIDs), whose tolerability is quite limited, despite being reported to be effective in reducing inflammatory urinary symptoms and pain [25,26]. In this context, phytotherapy has a role: herbal products can be effective against the symptoms of chronic prostatitis without causing significant toxicity [6,7,27–31]. Nonetheless, even phytotherapy drugs should be prescribed cautiously, particularly when they are used in association formulas.

Among the multifaceted phytotherapy groups, colostrum represents a novel treatment [32]. Previous in vivo studies have shown its anti-inflammatory activity [8,33], and colostrum has been successfully tested in vivo, both in gynecological and urological contexts [10,11].

In the present study, we are the first to show the efficacy and tolerability of PROSTYM®, an oral combination of immunoglobulins from bovine colostrum, *Serenoa repens* extracts and other anti-inflammatory elements, in chronic nonbacterial CP/CPPS patients. The main strength of this study was the accurate patient selection, together with its prospective design. In particular, we performed a thorough clinical evaluation and set a questionnaire cutoff (NIH-CPSI pain domain > 5) for inclusion in the study group. Moreover, the Meares

and Stamey test was administered to all patients during the initial diagnostic work-up to differentiate chronic bacterial prostatitis from nonbacterial prostatitis [16]. We also used validated questionnaires at each time point to evaluate the response to therapy, as reported in the previous literature reports [7,27], for an objective evaluation of our results.

The outcomes of our study revealed a significant improvement in pain after 3 months of daily treatment with PROSTYM®. Consequently, patient-reported quality of life improved as well, as demonstrated by the results of specific validated questionnaires such as the CPSI "quality of life" domains. On the contrary, despite being statistically significant, these questionnaire modifications could be of questionable clinical relevance. However, several clinically relevant improvements were observed, particularly regarding the CPSI total score at 3 months [20]. The activity of different compounds was reasonably responsible for this improvement: colostrum proteins, together with *Serenoa repens*, could have exerted anti-inflammatory activity, particularly within the prostatic tissue, thus reducing the global burden of urinary symptoms [11,12]. After 6 months of treatment, these benefits were substantially maintained. A slight but not significant rebound of pain was registered compared with the 3-month results. Urinary symptoms were mildly improved at 6 months compared to baseline, confirming the beneficial role of PROSTYM® in the medium term to control the entire spectrum of CP/CPPS symptoms, despite a non-negligible trend showing a better immediate response on pain control, followed by a flattening of the improvement curve and a globally milder and slower improvement of urinary symptoms. Our findings support those reported in previous studies concerning the role of phytotherapy for the treatment of CP/CPPS. In particular, similar rates of pain reduction have been reported in high-level, controlled studies investigating flower pollen extracts [7,27,29,30].

Concerning the safety of PROSTYM, we did not report any major adverse events, and the treatment was well tolerated by most patients for the 6-month duration. Pending the limit of not adopting a validated scale or criteria for adverse events, the only withdrawals were due to gastrointestinal intolerance that was attributed to the administration of the compound. One of the main issues of medium- and long-term treatments is patient adherence, which might also be affected by therapy costs. Nevertheless, in our study, only three patients (7.1%) discontinued the treatment and were lost to follow-up.

We must acknowledge several major limitations that affect this study. The absence of a comparative arm prevents us from excluding the influence of the placebo effect, which can represent a major issue when referring to treatments related to CP/CPPS. Particularly, in the absence of a randomized controlled trial setting, the clinical efficacy of the compound could be associated with a placebo effect or a spontaneous remission of symptoms over time. Moreover, a longer follow-up would be needed to assess the long-term effect of this treatment. It would be interesting to evaluate if the benefits of the treatment with PROSTYM® are related to its daily administration or last beyond its discontinuation. The relatively small sample size is another possible limitation of our study. Also, given the results of this preliminary investigation, we cannot exclude a certain risk of underpowering. A future proper RCT study with larger numbers will be advisable. Finally, the PROSTYM® compound contains multiple active components, beyond the most renowned colostrum immunoglobulins and *Serenoa repens* extract. In our study, we investigated the overall clinical activity of the PROSTYM®, while the effect of every single component could not be separated from the others. Overall, our study suggested positive effects of the use of PROSTYM in a novel setting in CP/CPPS patients. Therefore, our results could lead to a new therapeutic scenario, after the one depicted by a previous report on BPH patients [11]. The oral combination of colostrum and *Serenoa repens* appeared effective and safe for the treatment of pain and urinary symptoms related to chronic nonbacterial prostatitis, and its

daily administration produced a significant, persistent benefit after 3 and 6 months in a majority of our patients.

5. Conclusions

In this preliminary observational investigation, the daily oral administration of bovine colostrum, *Serenoa repens* and other anti-inflammatory elements showed a potential in improving pain and other urinary symptoms and was generally well tolerated by patients affected by CP/CPPS. To confirm the role of these compounds, future prospective, randomized, placebo-controlled studies are awaited.

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Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The datasets generated during and/or analyzed during the current study are not publicly available due to patient privacy protection issues but are available from the corresponding author upon reasonable request.

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Abbreviations

The following abbreviations are used in this manuscript:

CP/CPPS	Chronic prostatitis/chronic pelvic pain syndrome
LUTS	Lower urinary tract symptoms
BPH	Benign Prostatic Hyperplasia
CPSI	Chronic prostatitis symptom index
NPRS	Numeric Pain Rating Scale
IQR	Inter-Quartile Range
IPSS	International Prostate Symptom Score
IIEF5	International Index of Erectile Function (5 items)

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