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Efficacy and Safety of a Natural Supplement Containing Serenoa Repens, Solanum Lycopersicum, Lycopene, and Bromelain in Reducing Symptoms of Chronic Prostatitis/Chronic Pelvic Pain Syndrome: A Prospective Cohort Study in 250 Patients

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Abstract: Background: Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III is a widespread condition affecting men universally, with existing treatments showing limited success. This study evaluated the efficacy and safety of a natural supplement, composed of Serenoa repens, Solanum lycopersicum, lycopene, and bromelain, in managing symptoms of this condition among a substantial patient group. Methods: In this prospective study, 245 patients diagnosed with Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III were treated with the aforementioned supplement, alongside lifestyle alterations, such as refraining from spicy foods, alcohol, caffeine, and cycling, for a duration of three months. Patients' progress was assessed at one and three months using the National Institutes of Health Chronic Prostatitis Symptom Index (NIH-CPSI), the International Prostate Symptom Index (IPSS), quality of life (QoL) scores, and changes in total prostate-specific antigen (PSA) levels. Results: The supplement was well received with no serious adverse events reported. Significant improvements were observed in NIH-CPSI scores, IPSS, QoL scores, and a substantial decrease in total PSA levels at three months compared to baseline, with a positive trend noted from one-month to three-month evaluations. This was consistent in either patients with predominantly voiding or storage urinary symptoms. Conclusions: Our results suggest that this natural supplement in conjunction with lifestyle changes could offer a safe and effective alternative treatment for patients suffering from Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III. However, these findings require validation through further large-scale randomized controlled trials.

Keywords: chronic prostatitis/chronic pelvic pain syndrome NIH-class III; inflammation; Phytotherapy; Serenoa repens; Solanum lycopersicum; lycopene; bromelain

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1. Introduction

Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III, also known as Category III chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS), is a common and debilitating urological condition that affects men of all ages [1]. Despite various treatment

options available, including antibiotics, α-blockers, and anti-inflammatory agents [2], managing Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III remains a challenge due to its complex etiology and the heterogeneous nature of the disease [3,4]. Phytotherapy, the use of plant-derived supplements, has gained increasing attention in the management of urological disorders, including Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III [5].

Serenoa repens, also known as saw palmetto, is a widely used natural supplement in the treatment of lower urinary tract symptoms (LUTS) and benign prostatic hyperplasia (BPH) [6]. The modulation of inflammatory mediators and oxidative stress driven by Serenoa repens extracts could potentially lead to improvements in symptoms and chronic prostate inflammation. Nonetheless, studies have shown that Serenoa repens, when combined with selenium and lycopene, can provide significant improvement in voiding dysfunctions associated with chronic prostatitis [7]. Several evidences suggest that the oral administration of lycopene reduces inflammatory markers, such as interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNF-α), highlighting its potential in modulating the inflammatory response within the prostate gland. Additionally, the antioxidant capacity of lycopene may protect against oxidative stress-induced damage in the prostate, contributing to the management of chronic prostatitis [8].

Solanum lycopersicum, which is a potent antioxidant found in tomatoes, has been shown to exhibit therapeutic activity against chronic prostatitis, particularly when used as an adjunct to standard antibiotic treatment. In this context, a recent report outlined the efficacy of the combined treatment of NAC, bromelain, vitamin C, blackcurrant, resveratrol, and pelargonium with fluoroquinolones for the treatment of patients affected by chronic bacterial prostatitis, showing significant improvements in terms of pain, urinary symptoms, and quality of life in both IPSS and NIH-CPSI scores compared with fluoroquinolones alone [9].

Bromelain, an enzyme derived from pineapple stems, possesses anti-inflammatory and analgesic properties and can inhibit pro-inflammatory cytokines and reduce neutrophil infiltration into prostatic tissues, potentially leading to a reduction in prostatic inflammation. Furthermore, bromelain's immunomodulatory properties may restore the balance between pro-inflammatory and anti-inflammatory mediators, offering potential benefits in chronic prostatitis management, which may contribute to symptom relief in patients with Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III [10].

While the individual effects of these natural compounds have been explored, the potential synergistic effects of combining Serenoa repens, lycopene, Solanum lycopersicum, and bromelain in chronic prostatitis management require further investigation. Given the potential benefits of combining these natural supplements, this prospective case series study aimed to examine the efficacy and safety of a natural supplement containing Serenoa repens, Solanum lycopersicum, lycopene, and bromelain in reducing symptoms of Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III in a large cohort of patients. The aim of the present study was to assess the efficacy and safety of this natural supplement in reducing symptoms of Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III in patients who had previously shown inadequate response to conventional treatments or were seeking alternative therapies.

2. Materials and Methods

2.1. Study Design and Participants

This prospective case series study was conducted at a single tertiary urology center between January 2022 and December 2022. The study enrolled 245 male patients aged 18 to 65 years who were diagnosed with Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III (Category IIIa and IIIb) according to the National Institutes of Health (NIH) classification system [1]. Patients were eligible for enrollment if they had a history of prostatitis symptoms for at least three months, an NIH-CPSI score of $\geq$15, and a negative urine culture. A trial with an α of 5% and 80% power that required 240 patients was designed.

Patients were also divided into two categories of voiding and storage symptoms based on their IPSS subscores. Patients with predominantly obstructive symptoms (such as hesitancy, intermittency, weak stream, straining, and prolonged micturition) were classified as having voiding symptoms, while patients with predominantly irritative symptoms (such as urgency, frequency, and nocturia) were classified as having storage symptoms. Patients who reported both obstructive and irritative symptoms were classified according to the predominant symptomatology reported on the IPSS.

Patients with acute bacterial prostatitis, chronic bacterial prostatitis, prostate cancer, and any other significant urologic or medical conditions were excluded. Informed consent was obtained from all participants before enrollment.

2.2. Intervention

All patients received a natural supplement (PERLAPROST® soft gel) containing Serenoa repens extract (320 mg), Solanum Lycopersicum extract (100 mg), lycopene (15 mg), and bromelain (80 mg) daily for three months. Patients took two capsules daily, one in the morning and one in the evening, with meals. Additionally, patients were advised to make lifestyle adjustments, such as avoiding spicy foods, alcohol, caffeine, and cycling, to mitigate potential triggers of prostatitis symptoms.

2.3. Outcome Measures

The primary outcome measures were changes in the National Institute of Health Chronic Prostatitis Symptom Index (NIH-CPSI), International Prostate Symptom Score (IPSS), and quality of life (QoL) scores from baseline to one and three months after treatment initiation. The NIH-CPSI consists of three domains: pain, urinary symptoms, and quality of life/impact on daily activities [11]. The IPSS is a validated questionnaire to assess lower urinary tract symptoms (LUTS) and includes a QoL item [12]. The secondary outcome measure was the change in total prostate-specific antigen (PSA) levels from baseline to three months.

2.4. Assessments and Follow-Up

Patients were evaluated at baseline, one month, and three months after treatment initiation. At each visit, the NIH-CPSI, IPSS, and QoL scores were collected, and a digital rectal examination (DRE) was performed. Total PSA levels were measured at baseline and three months. Adverse events were recorded and assessed for severity and relationship to the intervention.

2.5. Statistical Analysis

Descriptive statistics, including means and standard deviations for continuous variables and frequencies for categorical variables, were used to summarize the patient demographics and baseline characteristics. Paired t-tests were used to compare the primary outcome measures (NIH-CPSI, IPSS, and QoL scores) and secondary outcome measure (total PSA levels) at baseline, one month, and three months after treatment initiation. The mean differences and 95% confidence intervals were calculated for each outcome measure. In addition, a subgroup analysis was performed to evaluate the treatment response in patients with voiding versus storage symptoms.

The proportion of patients with adverse events was calculated, and the severity and relationship to the intervention were assessed. A p-value of < 0.05 was considered statistically significant. All statistical analyses were performed using SPSS version 26.0 (IBM Corp., Armonk, NY, USA).

3. Results

3.1. Patient Demographics and Baseline Characteristics

A total of 245 patients were included in the study, with a mean age of 46.7 $\pm$ 11.2 years and a mean prostate volume of 34.6 $\pm$ 9.4 cc. The mean total PSA level was 3.25 $\pm$ 1.1 ng/mL.

Of the total cohort, 182 (74.2%) presented with voiding symptoms and 63 (25.8%) had storage symptoms.

At baseline, the overall cohort had a mean NIH-CPSI score of 20.3 ± 5.6, an IPSS score of 19.5 ± 3.8, and a QoL score of 3.8 ± 0.7. Upon subgroup analysis, patients with voiding symptoms had a mean NIH-CPSI score of 22.5 ± 5.2, while those with storage symptoms had a mean score of 18.5 ± 5.2. Patients with voiding symptoms also had a mean IPSS score of 19.6 ± 4.8, while those with storage symptoms had a mean score of 20.1 ± 5.1. The mean QoL score was 5.6 ± 1.9 for both subgroups. Patients' characteristics are detailed in Table 1.

Table 1. Baseline demographic and clinical characteristics of the patients.

Characteristic	Overall Cohort (n = 245)	Voiding Symptoms (n = 43)	Storage Symptoms (n = 202)
Number of Patients	245	182	63
Age (years)	46.7 ± 11.2	47.1 ± 11.5	45.5 ± 10.4
Prostate Volume (cc)	34.6 ± 9.4	35.1 ± 9.6	33.2 ± 8.2
Total PSA (ng/mL)	3.25 ± 1.1	3.12 ± 1.0	3.72 ± 1.3
NIH-CPSI Score (Baseline)	20.3 ± 5.6	22.5 ± 5.2	18.5 ± 5.2
Pain subscore	9.1 ± 2.8	9.6 ± 3.0	8.0 ± 1.8
Urinary subscore	6.7 ± 2.1	6.4 ± 2.2	7.3 ± 1.7
Quality of Life subscore	4.5 ± 1.4	4.4 ± 1.5	4.8 ± 1.1
IPSS (Baseline)	19.5 ± 3.8	19.6 ± 4.8	20.1 ± 5.1
Voiding subscore	11.4 ± 2.5	11.5 ± 2.9	11.1 ± 1.8
Storage subscore	8.1 ± 2.2	8.1 ± 2.1	8.2 ± 2.5
QoL (Baseline)	5.6 ± 1.9	5.6 ± 1.9	5.6 ± 1.9

3.2. Treatment Tolerability and Adverse Events

The natural supplement containing Serenoa repens, Solanum lycopersicum, lycopene, and bromelain was well tolerated by the patients, with no serious adverse events reported. Mild and transient side effects, such as gastrointestinal discomfort and headache, were experienced by 4% of the patients. However, these side effects did not lead to treatment discontinuation.

3.3. Primary and Secondary Outcomes

A significant improvement in the patients' symptoms was reported after three months of treatment. The one-month evaluation also revealed a favorable trend that continued to the three-month assessment.

Regarding the specific outcomes, the NIH-CPSI score decreased from a baseline value of 20.3 ± 5.6 to 13.2 ± 4.8 after three months of treatment, with a mean difference of −7.1 ± 6.1 ($p < 0.001$) (Figure 1A). The IPSS score also improved significantly, decreasing from a mean baseline value of 19.5 ± 3.8 to 14.3 ± 2.9 at three months (mean difference of −4.2 ± 4.0, $p = 0.02$) (Figure 1B). The QoL score showed a similar improvement, with a mean baseline value of 3.8 ± 0.7 and a mean value of 2.6 ± 0.5 at three months (mean difference of −1.2 ± 0.9, $p = 0.03$) (Figure 1C).

Furthermore, the study found a significant reduction in total PSA levels after three months of treatment, with a mean baseline value of 2.9 ± 1.1 ng/mL and a mean value of 1.9 ± 0.8 ng/mL at three months (mean difference of −0.6 ± 0.4, $p = 0.03$). Additionally, a substantial decrease in total PSA levels was observed at the end of the three-month treatment period compared to baseline values ($p < 0.001$) (Figure 1D).

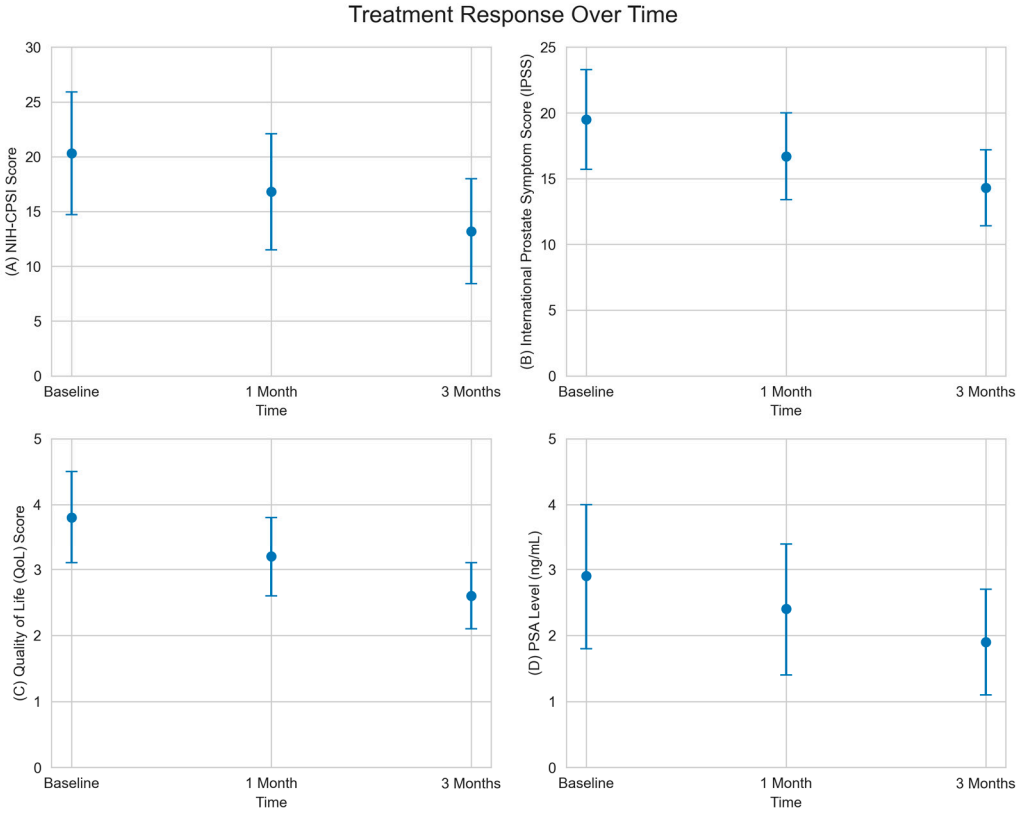

Figure 1. Patients response in terms of NIH-CPSI, IPSS, QoL scores, and in terms of total PSA level at baseline, 1st, and 3rd month evaluation.

3.4. Subgroup Analysis

A subgroup analysis was conducted to examine the treatment response in patients with voiding versus storage symptoms. As depicted in Table 2, the mean baseline scores for NIH-CPSI were 22.5 (SD = 5.2) for patients with voiding symptoms and 18.5 (SD = 5.2) for those with storage symptoms. After three months of treatment, both groups showed significant improvements in the NIH-CPSI, IPSS, and QoL scores compared to baseline values. The patients with voiding symptoms had a greater mean difference from baseline in NIH-CPSI score (−10.2, 95% CI = −11.3 to −9.1) compared to those with storage symptoms (−5.2, 95% CI = −11.3 to −9.1) ($p < 0.001$ in both groups).

The mean baseline IPSS scores were 19.6 (SD = 4.8) for patients with voiding symptoms and 20.1 (SD = 5.1) for those with storage symptoms. Both groups showed significant improvements in IPSS scores after three months of treatment ($p < 0.0001$), with the patients with voiding symptoms showing a greater mean difference from baseline (−5.2, 95% CI = −6.4 to −3.9) compared to those with storage symptoms (−5.0, 95% CI = −6.1 to −3.1).

For QoL scores, the mean baseline scores were similar for both groups (5.6, SD = 1.9), and both groups showed significant improvements in QoL scores after three months of treatment (Voiding Symptoms Group: $p = 0.04$; Storage Symptoms Group: $p = 0.02$). The patients with voiding symptoms had a greater mean difference from baseline in QoL score (−3.2, 95% CI = −3.6 to −2.6) compared to those with storage symptoms (−2.8, 95% CI = −3.3 to −2.5).

Overall, the subgroup analysis revealed that patients with voiding symptoms had a better treatment response compared to those with storage symptoms. However, both groups showed significant improvements in their symptoms after three months of treatment.

Table 2. Subgroup Analysis of Treatment Response in Patients with Voiding and Storage Symptoms of Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III.

Outcome Measure		**Voiding Symptoms (n = 202)**	**Storage Symptoms (n = 43)**
NIH-CPSI	Mean baseline score (SD)	22.5 (5.2)	18.5 (5.2)
	Mean 1-month score (SD)	16.7 (4.2)	16.7 (4.2)
	Mean 3-month score (SD)	12.3 (3.8)	13.3 (3.8)
	Mean difference from baseline (95% CI)	−10.2 (−11.3 to −9.1)	−5.2 (−11.3 to −9.1)
IPSS	Mean baseline score (SD)	19.6 (4.8)	20.1 (5.1)
	Mean 1-month score (SD)	15.7 (4.2)	16.3 (3.8)
	Mean 3-month score (SD)	14.4 (3.4)	13.4 (4.1)
	Mean difference from baseline (95% CI)	−5.2 (−6.4 to −3.9)	−5.0 (−6.1 to −3.1)
QoL	Mean baseline score (SD)	5.6 (1.9)	5.6 (1.9)
	Mean 1-month score (SD)	3.4 (1.5)	3.6 (1.5)
	Mean 3-month score (SD)	2.4 (1.2)	2.8 (1.3)
	Mean difference from baseline (95% CI)	−3.2 (−3.6 to −2.6)	−2.8 (−3.3 to −2.5)

4. Discussion

Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III is a common urological condition that affects men of all ages, and its management remains a challenge despite the variety of treatment options. In this study, we investigated the efficacy and safety of a natural supplement containing Serenoa repens, Solanum lycopersicum, lycopene, and bromelain in reducing symptoms associated with Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III. Our results suggest that the natural supplement, in combination with lifestyle modifications, is a safe and effective treatment option for patients with Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III.

After three months of treatment, we observed a significant improvement in the NIH-CPSI, IPSS, and QoL scores compared to baseline. These findings are consistent with previous studies investigating the efficacy of the individual components of this natural supplement [13]. For example, Serenoa repens has been found to improve IPSS and QoL scores in patients with lower urinary tract symptoms secondary to BPH [14]. Similarly, lycopene was found to be beneficial in reducing symptoms associated with chronic prostatitis in a randomized study [15]. Additionally, a combination of Serenoa repens, selenium, lycopene, bromelain, and methyl-sulfonyl-methane extracts was found to have a significant effect on all three evaluated scores compared to antibiotic treatment alone in a randomized study [8].

Pelvic pain is the main symptom and primary feature of CP, which may be often triggered in both urinary and ejaculatory episodes, with negative impact on LUTS, sexual activity, and then QoL [12]; consequently, pain relief is a predominate feature for the management of patients with CP. Nevertheless, no single etiological explanation has been put forward to account for the pelvic pain. According to a recent comparative study, carried out both in vitro and in vivo, SR exhibited similar levels of efficacy in reducing nuclear factor-kappa B binding activity and inhibiting the expression of cyclooxygenase and prostaglandin, both of which are known to be involved in inflammatory pain [16].

We also observed a significant decrease in total PSA levels at three months compared to baseline, which suggests a reduction in prostate inflammation. The natural supplement was well-tolerated by the patients, with only mild and transient side effects reported. We observed a high compliance rate among our patients, indicating that the natural supplement was acceptable for long-term use.

Our findings also support the results of a previous study that evaluated the efficacy of the same natural supplement in the management of benign prostatic hyperplasia (BPH) [17]. This study confirms that the natural supplement is effective in reducing symptoms associ-

ated with Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III and improving patients' QoL. One possible explanation for the effectiveness of this natural supplement in managing Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III could be its anti-inflammatory, antioxidant, and antiandrogenic effects. Chronic inflammation is a common feature of Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III, and oxidative stress has also been implicated in the pathogenesis of this condition [18,19]. Serenoa repens and lycopene, two components of the natural supplement, have been shown to have anti-inflammatory and antioxidant properties, respectively [20,21]. Additionally, Serenoa repens has antiandrogenic effects that may contribute to its beneficial effects on prostate symptoms [22].

These effects could potentially explain the observed improvements in the NIH-CPSI, IPSS, and QoL scores.

Moreover, the urinary symptoms domain appeared to make the most significant contribution to the NIH-CPSI; similar observations were reported in another study evaluating the effects of SRE in patients with LUTS/BPH [17]. According to early findings reported by the Medical Therapies of Prostate Symptoms (MTOPS) study and the REDUCE (Reduction by Dutasteride of Prostate Cancer Events) population, there are evidences of chronic prostate inflammation being relevant with LUTS [23], and chronic inflammation was also associated with symptom progression in patients with CP/CPPS. In a randomized biopsy study, SR treatment was reported to reduce prostatic inflammation, as determined by the measurement of T-lymphocyte markers, B-lymphocyte markers, and macrophage markers. Furthermore, it has also been reported that SR exhibits α1-adrenoceptor-inhibitory properties [23,24]; in combination with its chronic anti-inflammatory ability, these properties may facilitate the continuous improvement in urinary symptoms. A recent systematic review and meta-analysis found that SR could effectively increase urinary flow and improve urinary symptoms, and that it exhibited comparable efficacy to tamsulosin and short-term 5 α-reductase inhibitors in terms of relieving LUTS.

Another potential mechanism underlying the observed improvements could be the natural supplement's possible anti-cancer properties. Elevated PSA levels have been associated with an increased risk of prostate cancer, and the observed decrease in total PSA levels after treatment with the natural supplement could suggest a reduction in prostate inflammation and potentially a decrease in the risk of prostate cancer [21].

The subgroup analysis performed in this study aimed to evaluate the treatment response in patients with voiding versus storage symptoms of Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III. The results showed that both groups had significant improvements in the NIH-CPSI, IPSS, and QoL scores after three months of treatment with the natural supplement containing Serenoa repens, Solanum lycopersicum, lycopene, and bromelain. However, patients with voiding symptoms showed a slightly better response than those with storage symptoms. These findings suggest that the natural supplement may be more effective in managing voiding symptoms in patients with Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III. This information could be useful in clinical practice to help physicians tailor treatment approaches based on the predominant symptomatology of the patient. Further studies with larger sample sizes and longer follow-up periods are needed to confirm these findings and determine the long-term effectiveness of the natural supplement in managing Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III.

Despite the promising results of our study, several limitations need to be considered. The study lacked a control group, which limits the ability to draw definitive conclusions about the effectiveness of the natural supplement. The study also had a relatively short follow-up period of three months, and longer follow-up periods are needed to evaluate the long-term effectiveness of the natural supplement. Moreover, the presence of potential confounding factors, such as patient lifestyle adjustments, might have introduced several non-negligible biases in the reported results. The dropout rate in our study was low, but it could still have influenced the analysis. The lack of a standardized protocol and outcome

measurements may have led to outcome bias. Finally, our study did not investigate the mechanisms underlying the observed improvements in symptoms and PSA levels. Further studies will assess in a multicentre setting the effects of PERLAPROST® soft gel oral supplementation after a 12–24 months follow up comparing with a naive-patients control group. Patients will receive a dedicated lifestyle counselling to account potential confounding factors. Future studies with a well-designed control group evaluation and a longer follow-up are still warranted to assess the reliability of our reported results.

In conclusion, our study provides evidence that a natural supplement containing Serenoa repens, Solanum lycopersicum, lycopene, and bromelain, along with lifestyle modifications, is a safe and effective treatment option for patients with Chronic Prostatitis/Chronic Pelvic Pain syndrome NIH-class III. The observed improvements in symptoms and PSA levels could be explained by the natural supplement's anti-inflammatory, antioxidant, antiandrogenic, and possibly anti-cancer properties. Further studies are needed to confirm the long-term effectiveness and safety of this natural supplement and to investigate the mechanisms underlying its observed effects.

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