Boswellia resin extract and propolis derived polyphenols in patients with type III chronic prostatitis/chronic pelvic pain syndrome: An Italian prospective multicenter study

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Abstract  Objective: To assess the efficacy and safety of a treatment regimen based on rectal administration of Boswellia resin extract and propolis derived polyphenols in patients with type IIIa and type IIIb chronic prostatitis and chronic pelvic pain syndrome (CP/CPPS).

Methods: Patients with type IIIa and type IIIb CP/CPPS received one rectal suppository a day for 15 days per month for 3 consecutive months. Participants were evaluated with National Institutes of Health-Chronic Prostatitis Symptom Index (NIH-CPSI), the International Prostate Symptom Scores (IPSS), International Index of Erectile Function (IIEF), four-glass test, uroflowmetry, and prostate-specific antigen assessments at baseline and at Week 4, and Week 12. Primary endpoints were improvement in pain domain of NIH-CPSI and improvement of NIH-CPSI total score. Secondary outcomes included improvement of micturition and quality of life (QoL) domains of NIH-CPSI questionnaire.

Results: A total of 61 males were enrolled. No adverse events were reported. Significant improvements from baseline to Day 30 were reported for NIH-CPSI total score (mean difference: /C0 9.2; \( p < 0.01 \)), NIH-CPSI pain domain (mean difference: /C0 5.5; \( p < 0.01 \)), NIH-CPSI micturition domain, NIH-CPSI QoL domain, and IPSS total score (mean difference: /C0 5.6; \( p < 0.01 \)). No significant changes from baseline in terms of IIEF score or maximum flow rate were observed. At
1. Introduction

Chronic prostatitis (CP) is a highly prevalent condition affecting 11%–14% of men of all ages, accounting for about 12% of all urological consultations in Western countries [1–3]. The key symptom of CP is pelvic pain possibly associated with lower urinary tract symptoms (storage and/or voiding difficulties), ejaculatory pain, erectile dysfunction, and haematospermia [4]. Patients with CP experience a negative impact on their quality of life (QoL) comparable to men with unstable angina, recent myocardial infarction, or active Crohn’s disease [4,5]. Despite the high prevalence and morbidity of this condition, CP remains a poorly understood clinical entity. Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is diagnosed when pelvic pain existing for at least 3 months of the preceding 6 months and no other recognizable causes have been identified [4]. It remains uncertain whether CP can be connected in all cases to prostatic involvement hence the alternate denomination (chronic pelvic pain syndrome). CP/CPPS is sub-classified as type IIIa (inflammatory), and type IIIb (non-inflammatory), according to the presence of white blood cell in prostatic secretions [6,7].

CP/CPPS represents the vast majority of clinical scenario, accounting for 90%–95% of all prostatitis cases [3]. To assess in a standardized way symptoms’ severity and its evolution after treatment, Chronic Prostatitis Collaborative Research Network (CPCRN) proposed a questionnaire named National Institute of Health-Chronic Prostatitis Symptom Index (NIH-CPSI), which evaluated three domains: Pain, voiding symptoms, and impact on QoL [8]. Long-term antibiotic administration is the habitual therapy for bacterial prostatitis, while CP/CPPS is one of the most challenging urological conditions because it lacks a standardized treatment regimen [7]. The aim of therapy is to ameliorate individual patient-reported symptoms by the use alone or in combination of several treatment modalities, including medical devices (substances based), phytotherapeutics, anti-inflammatory drugs, antibiotics, alpha1-blockers, biofeedback, and physical therapy in order to increase QoL [7].

Phytotherapy is gaining popularity for the treatment of many chronic conditions. In CP/CPPS management, a number of phytotherapeutic agents (cernitin pollen extract [extract of bee pollen], quercetin [a polyphenolic bioflavonoid], and saw palmetto [an herbal lipid-extract from the American dwarf palm tree]) have been utilized with mutable success, but rarely evaluated in appropriate clinical trials [7]. Lastly medical devices represent another approach in the therapeutic field [7]. They do not exert their therapeutic activities through a pharmacological mechanism of action but in a chemical-physical way. They may have scavenger and anti-radical effects, and barrier effects against microorganisms and pathogens, creating a microenvironment not suitable for the normal proliferation of inflammation reactions and pathogenic microorganisms [7].

*Boswellia serrata* gum resin extracts (or olibanum) are used to treat inflammatory conditions in ayurvedic medicine, the traditional Indian medicine based on a holistic approach and consumption of medicinal herbs [9,10]. *In vivo* Boswellic acids exhibit anti-inflammatory properties in a variety of inflammatory diseases, including rheumatoid arthritis, osteoarthritis, and asthma [10–14]. In particular, a novel Boswellic acid formulation (lecithin, *Boswellia serrata* resin extract) has been synthetized for topical administration route and successfully tested in psoriatic and eczematous patients [9]. Propolis is another agent with promising anti-inflammatory actions [11] probably also based on its antioxidant capacity [11,12].

In light of these promising results, we conducted a prospective multicenter pilot study on a drug in the formulation of suppository, made up of these two elements (*Boswellia resin extract* and propolis derived polyphenols) to assess its efficacy and tolerability for the management of patients with type IIIa and type IIIb CP/CPPS.

2. Methods

2.1. Study design

This prospective, multicenter study was performed according to Good Clinical Practice from September 2019 to February 2020 in five Italian urologic centers to determine the safety and efficacy of a treatment regimen based on rectal administration of Boswellia resin extract and propolis derived polyphenols in patients with type IIIa and type IIIb CP/CPPS. The study protocol was in accordance with the guidelines for clinical trials in CP/CPPS described by the NIH CPCRN [15]. All procedures performed involving human participants were in accordance with the ethical standards of the institutional and national research committee (approval number 142511) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. All patients agreed and signed the informed consents; their information (including clinical
information and surveillance) would be collected for scientific study and be published in professional medical journals.

A category III CP/CPPS diagnosis was formulated through assessment of a detailed history and physical examination, standard microbiologic cultures, microscopic urinalysis according to Meares-Stamey test (before voided bladder 1 [VB1] and voided bladder 2 [VB2] and after prostatic massage voided bladder 3 [VB3]), prostatic secretion analysis, uroflowmetry, prostate ultrasonography, and residual urine volume measurement. The severity of urinary and sexual symptoms was assessed by use of validated questionnaires (NIH-CPSI, the International Prostate Symptom Scores [IPSS], and International Index of Erectile Function [IIEF]).

Inclusion criteria were: Patients between 18 and 75 years of age with symptoms of CP/CPPS for at least 3 months during the 6 months before enrolment; a score in the pain domain of the Italian-validated version of the NIH-CPSI ≥7; a total NIH-CPSI score ≥15.

Exclusion criteria were: Confirmed urinary tract infection; history of epididymitis or sexually transmitted disease; history of urethritis, with discharge 4 weeks prior to study admission; acute bacterial or chronic bacterial prostatitis at study admission (bacteriuria $\geq 10^6$ colony-forming units [CFU]/mL in mid-stream urine or $\geq 10^3$ CFU/mL in VB3); residual urine volume >50 mL; history of urogenital cancer; indication for or history of prostate surgery, including prostate biopsy; treatment with phytotherapeutics, alpha-blockers, or antibiotics 4 weeks prior to study entry; and treatments with drugs affecting intraprostatic hormone metabolism 6 months prior to study admission. The above-mentioned medications were not allowed during the full study course, nor were any other complementary pharmacological agents that could impact the study objectives.

### 2.2. Study procedure

All patients enrolled in the study received the same treatment regimen consisting of one rectal suppository a day for 15 days per month for 3 consecutive months.

NIH-CPSI score (0–43) with its subscales (pain domain [0–21], micturition domain [0–10], and QoL domain [0–12]), and IIEF (6–30), IPSS (0–35), mean and maximum urinary flow rate, and residual urine volume were evaluated at Week 0 (before start of study drug), Week 4, and Week 12 (end of study drug). Adverse events were recorded during the entire course of study.

### 2.3. Statistical analysis

Primary endpoints of the study were symptomatic improvement in the pain domain of the NIH-CPSI and symptomatic improvement of the NIH-CPSI total score. Secondary outcomes included symptomatic improvement of the micturition and QoL domains of the NIH-CPSI questionnaire.

To compare the response in the treatment group, the non-parametric Wilcoxon test was used. All the analysis was done with statistical analysis system SPSS software, version 11.0 (SPSS, Inc., Chicago, IL, USA) with $p<0.05$ considered as statistically significant.

### 3. Results

A total of 61 males (median age of 61.0 years, interquartile range: 52.5–64.0 years) have been enrolled in this study. Patients have been revaluated 1 month and 3 months after starting treatment. All enrolled patients completed the treatment and performed the protocol follow-up checks. No adverse events have been reported. Table 1 lists the characteristics of the enrolled population at baseline.

### Table 1. Characteristics of the enrolled population at baseline.

| Variable | Overall (n=61) | IIIa $^a$ (n=31) | IIIb $^b$ (n=30) |
|----------|----------|----------|----------|
| Age $^c$, year | 61.0 (52.5–64.0) | 59.0 (45.0–63.0) | 61.0 (53.7–66.5) |
| PSA $^a$, ng/mL | 2.9 (1.6–3.5) | 2.9 (1.1–3.9) | 2.5 (1.6–3.2) |
| IPSS total $^a$, year | 18.0 (12.0–23.5) | 22.0 (18.0–25.0) | 15.5 (11.7–20.0) |
| Voiding | 5.0 (3.0–6.0) | 5.0 (4.0–6.0) | 4.0 (3.0–7.0) |
| Storage | 12.0 (8.0–16.5) | 15.0 (12.0–20.0) | 11.0 (8.0–14.0) |
| IIEF score $^c$ | 18.0 (15.0–21.0) | 19.0 (17.0–22.0) | 15.5 (12.0–20.0) |
| NIH-CPSI total score $^c$ | 21.0 (18.0–24.0) | 23.0 (21.0–29.0) | 19.5 (18.0–21.0) |
| Pain | 9.0 (8.0–10.0) | 10.0 (8.0–12.0) | 9.0 (8.0–10.0) |
| Micturition | 5.0 (4.0–6.0) | 6.0 (5.0–7.0) | 4.0 (2.7–6.0) |
| Quality of life | 7.0 (5.0–9.0) | 9.0 (6.0–10.0) | 6.0 (5.0–7.0) |
| Prostate volume $^d$, mL | 44.0 (33.0–48.5) | 40.0 (33.0–47.0) | 45.0 (33.0–56.2) |
| Leukocytes in VB3 $^d$, mL | 20.0 (8.0–25.0) | 33.0 (12.0–45.0) | 8.0 (7.0–8.0) |
| Residual urine volume $^d$, mL | 30.0 (5.0–50.0) | 30.0 (20.0–45.0) | 25.0 (0–50.0) |
| Maximum flow rate $^d$, mL/s | 14.0 (11.2–18.0) | 12.0 (10.0–14.2) | 16.0 (14.0–19.0) |
| Mean flow rate $^d$, mL/s | 8.8 (7.0–10.0) | 8.9 (7.0–9.6) | 8.5 (7.0–10.0) |

**Abbreviations:** NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; VB3, voided bladder 3.

$^a$ Leukocytes in VB3 >10 (field of vision: 400×).

$^b$ Leukocytes in VB3 equal or less 10 (field of vision: 400×).

$^c$ Values are presented as median (interquartile range).

$^d$ Number of leukocytes seen at microscope (field of vision: 400×).
Significant improvements from baseline to Day 30 have been reported for NIH-CPSI total score (mean difference: −9.2; \(p<0.01\)), NIH-CPSI pain domain (mean difference: −5.5; \(p<0.01\)), NIH-CPSI micturition domain, NIH-CPSI QoL domain, and IPSS total score (mean difference: −5.6; \(p<0.01\)). We did not observe any significant change from baseline in terms of IIEF score and maximum flow rate. Data are summarized in Table 2, Fig. 1, and Fig. 2.

At final follow-up (Day 90), we reported a further significant improvement in terms of NIH-CPSI total score (mean difference: −12.2; \(p<0.01\)), NIH-CPSI pain domain (mean difference: −6.6; \(p<0.01\)), NIH-CPSI micturition domain, and NIH-CPSI QoL domain. Data have been described in detail in Table 2, Fig. 1, and Fig. 2.

A definite and important clinical improvement over baseline can be determined by a decrease of 25% or 6 points decrease in NIH-CPSI total score \([15–18]\). At Day 30, 72% of the patients had achieved this goal. After 90 days the percentage had risen to 92% (Fig. 3).

The enrolled population has been also subcategorized in type IIIa and type IIIb CP/CPPS according to the number of leukocytes in VB3. Patients with type IIIa CP/CPPS (defined by leukocytes count [field of vision: 400\(\times\)] in VB3 >10) have showed a greater improvement in terms of NIH-CPSI total score, NIH-CPSI pain domain, NIH-CPSI micturition domain, NIH-CPSI QoL domain, and IPSS total score when compared with patients affected by type IIIb CP/CPPS. Data have been described in detail in Table 3, Fig. 4, and Fig. 5.

No side effects or causes for discontinuing treatment were found in this patient cohort during the entire study observation period.

### 4. Discussion

CP/CPPS is one of the most challenging urological conditions because it lacks a well-defined treatment regimen. Nowadays there are several strategies for its management using both non-pharmacological and pharmacological approaches \([7]\). Recently, Franco et al. \([7]\) have performed a very comprehensive meta-analysis on the interventions for treating CP/CPPS. They included 99 unique studies in 9119

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**Table 2** Clinical evolution after treatment in the enrolled population.

| Variable                      | Mean value at Day 30 (percentage of change from baseline) | Mean change±SE at Day 30 | Mean value at Day 90 (percentage of change from baseline) | Mean change±SE at Day 90 |
|-------------------------------|----------------------------------------------------------|--------------------------|----------------------------------------------------------|--------------------------|
| PSA, ng/mL                    | Not evaluated                                            | Not evaluated            | 2.3 (−20.7)                                              | −0.6±0.9                 |
| IPSS total score              | 12.4 (−31.1)                                             | −5.6±5.9                 | 10.1 (−43.9)                                             | −7.9±6.5                 |
| IIEF score                    | 18.5 (2.8)                                               | 0.5±1.5                  | 18.9 (5.0)                                               | 0.9±2.1                  |
| NIH-CPSI total score          | 11.8 (−43.8)                                             | −9.2±5.1                 | 8.8 (58.1)                                               | −12.2±6.3                |
| Pain                          | 3.5 (−61.1)                                              | −5.5±2.3                 | 2.4 (−73.3)                                              | −6.6±2.6                 |
| Micturition                   | 3.5 (−30.0)                                              | −1.5±1.7                 | 2.8 (−44.0)                                              | −2.2±2.3                 |
| Quality of life               | 5 (−28.6)                                                | −2.0±2.2                 | 3.8 (−45.7)                                              | −3.2±2.7                 |
| Leukocytes in VB3\(^a\)       | Not evaluated                                            | Not evaluated            | 4.1 (−79.5)                                              | −15.9±4.5                |
| Maximum flow rate, mL/s       | 15 (7.1)                                                 | 1.0±2.2                  | 15.3 (9.2)                                               | 1.3±2.3                  |

PSA, prostate-specific antigen; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; VB3, voided bladder 3; SE, standard error.

\(^a\) Number of leukocytes seen at microscope (field of vision: 400\(\times\)).

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patients with CP/CPPS, with evaluations of 16 types of pharmacological treatments. The investigators found low-to-very low-quality evidence that antibiotics, alpha-blockers, 5alpha-reductase inhibitors), anti-inflammatories, phytotherapy, traditional Chinese medications, and intraprostatic botulinum instillation may reduce prostatitis symptoms without a raised incidence of adverse events in the short-term, except for alpha-blockers, which may be correlated with a rise in mild adverse events [7,19]. Focusing on phytotherapeutics and medical devices, the most analysed products included in previous studies were calendula-curcuma suppositories [20], oral formulation of cranberry [21], quercetin [22], and pollen extract [18,23].

In clinical trials, these treatments showed some beneficial effects on clinical symptoms compared to placebo (NIH-CPSI score mean difference: 5.0 ± 2.4; 95% confidence interval: 6.8 ± 3.2), but the quality of evidence was low, due to unclear or high risk of bias in most domains in most studies, and imprecision (the confidence interval crosses the threshold for the minimal clinically important difference) [7].

With this knowledge in mind and in light of the strong anti-inflammatory activities of propolis and Boswellia

| Table 3 | Clinical evolution after treatment in the enrolled population according the category of type III CP/CPPS. |
|--------|----------------------------------------------------------------------------------------------------|
| Variable | Mean value at Day 30 (percentage of change from baseline) | Mean change ± SE at Day 30 | Mean value at Day 90 (percentage of change from baseline) | Mean change ± SE at Day 90 |
| PSA, ng/mL | IIla | Not evaluated | Not evaluated | 2.2 (24.1) | 2.1 (24.1) |
| IPSS total score | IIlb | Not evaluated | Not evaluated | 10.0 (56.4) | 9.9 (56.4) |
| IIEF | Not evaluated | Not evaluated | 13.6 (12.2) | 13.6 (12.2) |
| NIH-CPSI total score | Not evaluated | Not evaluated | 15.6 (30.8) | 15.6 (30.8) |
| Pain | Not evaluated | Not evaluated | 15.6 (30.8) | 15.6 (30.8) |
| Micturition | Not evaluated | Not evaluated | 7.9 (22.5) | 7.9 (22.5) |
| Quality of life | Not evaluated | Not evaluated | 3.4 (15.1) | 3.4 (15.1) |
| Leukocytes in VB3 | Not evaluated | Not evaluated | 3.5 (12.5) | 3.5 (12.5) |
| Maximum flow rate, mL/s | Not evaluated | Not evaluated | 20.2 (6.3) | 20.2 (6.3) |

PSA, prostate-specific antigen; IIEF, International Index of Erectile Function; IPSS, International Prostate Symptom Score; NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; VB3, voided bladder 3; SE, standard error.

Figure 3 Patients with important clinical improvement (decrease of 25% or 6 points in National Institutes of Health-Chronic Prostatitis Symptom Index total score) at Day 30 and Day 90 of treatment, respectively.

Figure 4 Mean change ± SE from baseline in NIH-CPSI total score at Day 30 and Day 90 of treatment in patients with type IIla and type IIlb chronic prostatitis/chronic pelvic pain syndrome, respectively. NIH-CPSI, National Institutes of Health-Chronic Prostatitis Symptom Index; SE, standard error.
compounds have been tested with benefit in previous 
Boswellia variously combined with other anti-inflammatory 
nize oxidant species thus decreasing painful symptoms, 
substances to be in contact with the mucosa and antago-
available, but transrectal way, which allows antioxidant 
administration of Boswellia resin extracts and propolis are 
no comparative data between the oral and transrectal 
transrectal administration. At the best of our knowledge, 
systemic bioavailability of these constituents after oral or 
significant anti-inflammatory activity.

repositories based formulation of propolis and Boswellia exert 
[11 e 14]. In fact, as observed by Sibona et al. [12], sup-
fec of its components; in fact, some studies showed the 
probably connected to the scavenger and antioxidant ef-
anti-inflammatory characteristics, and this activity is 
mostly benefit from the anti-inflammatory effect of 
IIIa and type IIIb CP/CPPS.

The main finding of this study was that this treatment is 
able to deliver early pain relief and ameliorate urinary 
symptoms and the QoL in men with CP/CPPS without severe 
side effects. In addition, we found that patients with type 
IIla CP/CPPS might receive more advantages when 
compared with type IIIb CP/CPPS patients, probably 
because males with greater inflammatory CP/CPPS may 
obviously benefit most from the anti-inflammatory effect of 
the compound. In support of this hypothesis, we found in 
the subgroup of patients with type IIla CP/CPPS a drastic 
reduction in the number of leukocytes in prostate secre-
tions after 3 months from the start of treatment when 
compared with those one with type IIIb CP/CPPS (leuko-
cytes [field of vision: 400 x] in VB3: -26.2±5.2 vs. 
-5.0±2.3, respectively) (Table 3). The rationale of this 
therapy could be various and mainly associated with its 
anti-inflammatory characteristics, and this activity is 
probably connected to the scavenger and antioxidant ef-
fect of its components; in fact, some studies showed the 
anti-inflammatory effect of antioxidant substances 
[11 e 14]. In fact, as observed by Sibona et al. [12], sup-
positories based formulation of propolis and Boswellia exert 
significant anti-inflammatory activity. 

We still have recognized inconclusive data about the 
 systemic bioavailability of these constituents after oral 
or transrectal administration. At the best of our knowledge, 
no comparative data between the oral and transrectal 
administration of Boswellia resin extracts and propolis are 
available, but transrectal way, which allows antioxidant 
substances to be in contact with the mucosa and antago-
nize oxidant species thus decreasing painful symptoms, 
seems reasonable [12]. In fact, suppositories based on 
Boswellia variously combined with other anti-inflammatory 
compounds have been tested with benefit in previous 
studies in men with chronic pelvic pain; in both cases they 
are medical devices [11 e 14].

The biological activities of propolis and Boswellia resin 
eextracts suggest intriguing possibilities for comparison and/ 
or combination with the other therapeutic options available 
for the treatment of patients with CP/CPPS, and this should 
be the topic of future studies.

Some limitations should be taken into account. First of 
all, it is a pilot study with a small sample size; however, the 
enrolled population was numerically in line with previous 
studies on other phytotherapeutic agents and medical de-
ve in addition, it was not a blinded study and there was 
no placebo group; nevertheless, the vast majority of the 
subjects (92% at Day 90, Fig. 3) reached a level of 
 improvement in symptoms (25% or 6-point decrease in NIH-
CPSI scores) universally recognized as important and diffi-
cult to associate with a random effect [15 e 18]. Moreover, 
the dosing scheme, although effective, is still investiga-
tional and will have to be confirmed in subsequent studies. 
Lastly, we did not examine markers of inflammation in the 
cohort, limiting our analysis to clinical results rather than 
laboratory findings.

On the opposite, some strengths of the study were the 
investigation of new agents for the management of CP/CPPS, 
rigorous inclusion criteria, and careful monitoring of treat-
ment through validated diagnostic tools.

Further study with greater sample size and a placebo 
group should be conducted to confirm these preliminary 
data.

5. Conclusion

This prospective multicenter study showed that a treat-
ment regimen based on rectal administration of Boswellia 
resin extract and propolis derived polyphenols ameliorated 
significantly total symptoms, pain, and QoL in men with CP/ 
CPPS (NIH category IIla/IIIB), probably for the high antiox-
idant capacity, without important side-effects. The ideal 
dosage regimen, superior efficacy compared to other 
therapeutic options, and long-term durability of the 
response should be confirmed in further studies.

Author contributions

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Conflicts of interest

The authors declare no conflict of interest.
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