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ORIGINAL PAPER

Serenoa repens associated with selenium and lycopene extract and bromelain and methylsulfonylmethane extract are able to improve the efficacy of levofloxacin in chronic bacterial prostatitis patients

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Summary

Objective: *To date, the management of patients with chronic bacterial prostatitis (CBP) is not satisfactory, especially in terms of symptoms relief. Here, we evaluated the efficacy and the safety of a combination of serenoa repens, selenium and lycopene extract + bromelain and methylsulfonylmethane extract associated with levofloxacin in patients with CBP.*

Materials and methods: *All patients with clinical and instrumental diagnosis of CBP, admitted to a single Urological Institution from March to June 2015 were enrolled in this phase III study. All enrolled patients were randomized into two groups: Group A received levofloxacin 500 mg o.d. for 14 days associated with lycopene and methylsulfonylmethane; Group B received levofloxacin (500 mg o.d. for 14 days) only. Clinical and microbiological analyses were carried out at the time of admission (T0) and during the follow-ups at 1 month (T1) and 6 months (T2) from the end of the treatment. NIH Chronic Prostatitis Symptom Index (CPSI), International Prostatic Symptom Score (IPSS) and Quality of Well-Being (QoL) questionnaires were used. The main outcome measures were the rate of microbiological cure and the improvement in questionnaire results from baseline at the end of the follow-ups period.*

Results: *Forty patients were enrolled in Group A and 39 in Group B. During the follow-up (T1), we recorded a significant changes in terms of NIH-CPSI and IPSS in Group A (mean difference: 17.6 ± 2.65; 12.2 ± 2.33; $p < 0.01$; $p < 0.05$, respectively) and versus Group B at the intergroup analysis (mean difference: -9 ± 1.82; -8.33 ± 1.71; $p < 0.05$; $p < 0.05$, respectively). No differences were reported in terms of microbiological findings between the two groups. At the second follow-up visit (T2), questionnaire results demonstrated statistically significant differences between groups ($p < 0.001$). One patient in Group A (2.5%) and 7 patients (17.9%) in Group B showed a symptomatic and microbiological recurrence ($p = 0.02$).*

Conclusions: *The combination of serenoa repens, selenium, lycopene + bromelain and methylsulfonylmethane extracts improved the clinical efficacy of levofloxacin in patients affected by CBP without the development of side effects.*

KEY WORDS: *Chronic bacterial prostatitis; Levofloxacin; Serenoa repens; Bromelain.*

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No conflict of interest declared.

INTRODUCTION

Even if the prevalence of chronic bacterial prostatitis (CBP), category II according to the National Institutes of Health (NIH) classification of *Chronic Prostatitis-Chronic Pelvic Pain Syndrome*, ranges in Europe between 7 and 14% of all cases with prostatitis (1-2), the impact on patient's quality of life is high (3-4). Although a long-term antibiotic treatment with fluorquinolones represents the gold standard therapy for CBP (5), short-term recurrences and drug-related adverse events are frequently reported (6-7). In this sense, the use of phytotherapy to both alleviate symptoms related to CBP and decrease the rate of symptomatic recurrence is nowadays increasing. It seems related toseveral reasons, e.g. low side-effect and costs (8), high level of adherence (9) and a low rate of efficacy of standard treatments with subsequent patient disappointment and drop-out (10). Several phytotherapeutic compounds have recently been investigated to treat or prevent bacterial prostatitis, such as *Serenoa repens*, *Urtica dioica*, or other compounds such as curcumin (11-13). Here, we focused our attention on *Serenoa repens*, *selenium*, *lycopene*, *bromelain* and *methylsulfonylmethane* extracts. The role of *Serenoa repens*, *selenium* and *lycopene* is well discussed in the current literature, with convinced results about their efficacy in the treatment of patients with prostatitis (11, 14-15). Recently, *Marzano et al.* showed the efficacy of a compound with *bromelain* in improving urinary symptoms related to benign prostatic hyperplasia (16). The efficacy of *bromelain* on prostatic symptoms is probably due to its anti-inflammatory effect by increasing the production of anti-inflammatory prostaglandins such as TNF-alfa or interleukin (IL)-6 (17).

Methylsulfonylmethane, also known as dimethylsulfone and methylsulfone, shows several positive effects on a variety conditions, such as osteoarthritis and allergic rhinitis (18). It is well known that IL-6 production is rapidly increased in acute inflammatory responses associated with infection, trauma, and other stresses (17). However, high-levels of IL-6 could induce an inflammatory state. *Karlsen et al.* demonstrated that *methylsulfonylmethane* inhibits IL-6

production in macrophage cells, and reduces plasma levels of IL-6 in animal model (17). On the basis of these evidences, the use of an association between antibiotic and anti-inflammatory compounds could represents a good option for the treatment of CBP patients.
Therefore, in the present study we evaluated the efficacy and the safety of a combination of *Serenoa repens*, *selenium*, *lycopene* (PROSTADEP PLUS®) and *bromelain*, *methylsulfonylmethane* (ZACHELASE®) associated with levofloxacin, to improve quality of life in patients with CBP.

Patients and methods

Study design

We performed a randomized, prospective, open-label, and parallel groups study in a single urological institution between March and June 2015. The study was conducted according to the ethical principles of the Declaration of Helsinki and the protocol was approved by an independent ethics committee. Before the beginning of the study, all participants signed the written informed consent. No placebo run-in period was considered necessary for the treatment of patients with urinary culture positivity.

Experimental protocol

All consecutive patients presented us for symptoms related to CBP and post-prostate massage urine culture positive for uropathogens were enrolled in this study. At the time of admission (T0), the patients underwent self-administered baseline questionnaire [NIH-Chronic Prostatitis Symptom Index (NIH-CPSI) and International Prostatic Symptom Score (IPSS)], urological examination with history interview and Meares-Stamey test performed by the same urologist (TC) in agreement with the European Association of Urology (EAU) guidelines (5). All patients underwent two follow-ups at 1 month (T1) and 6 months (T2) from the end of therapy. During each follow-up all patients underwent NIH-CPSI, IPSS questionnaires and urological examination. The Meares-Stamey test was carried-out only in patients with symptomatic recurrence. In agreement with our previous papers, the patients that were positive to Meares-Stamey test for uropathogens were treated with other antibiotics depending on the organism and its susceptibility profile (3, 11).

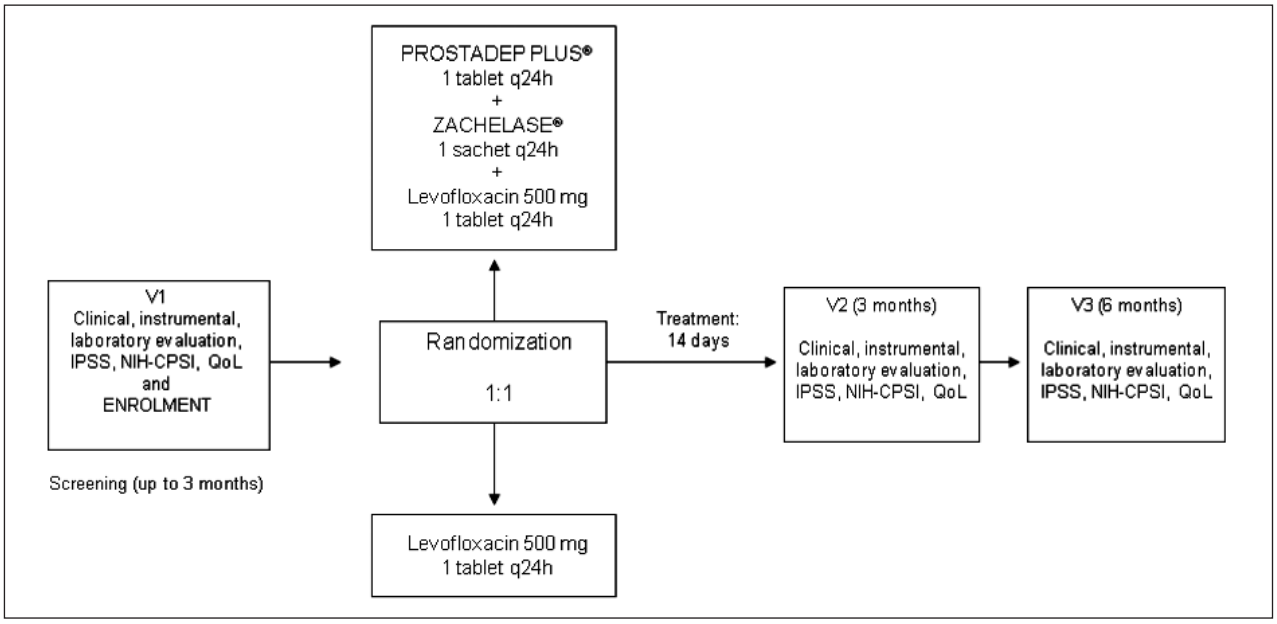
Inclusion and exclusion criteria

The primary inclusion criteria were age between 18 and 45 years and the following conditions: the presence of symptoms related to CBP for at least 3 months (5) and a positive Meares-Stamey 4-glass test with first voided urine, midstream urine, prostatic secretion and a VB3 urine culture, which had to be ≥ 103 colony forming units (CFU)/mL of uropathogens (5, 20). Patients with demonstrated or suspected allergy to fluoroquinolones or other compounds contained in the treatments were excluded. Moreover, patients treated in the last 4 weekswith antibiotics were also excluded. Patients with positive tests for atypical or sexually transmitted diseases, such as *Chlamydia trachomatis*, *Ureaplasma urealiticum*, or *Neisseria gonorrhoeae* were excluded. In order to obtain an homogenous group to analyze the following bacteria were considered as uropathogens, in accordance with *Trinchieri*: enteric Gram-negative rods; enterococci, *Staphylococcus saprophyticus*; and group B streptococci (20).

Questionnaires and urological examinations

The validated Italian versions of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) (21) and the International Prostatic Symptom Score (IPSS) (22) were administered to each patient. The questionnaire was self-administered when the patient arrived at the Centre.

Figure 1.
The figure shows the study schedule.
IPSS: International Prostatic Symptom Score; NIH-CPSI: NIH Chronic Prostatitis Symptom Index; QoL: Quality of Well-Being. V1: visit 1, at the enrolment; V2: visit 2 at the first follow-up; V3: visit 3 at the second follow-up.



Moreover, patient quality of life was measured by using an Italian version of the Quality of Well-Being, a validated, multiattribute health scale (23). This scale was selected because it has been successfully applied to acute illnesses, whereas other quality of life scales, including the Short Form-36 (SF-36) Health Survey, are more suitable in chronic cases. Higher scores on the QoL scale reflect a higher quality of life (24). In accordance with the study by *Nickel et al.*, prostatitis-like symptoms were considered significant at a pain score of ≥ 4. The NIH-CPSI was also used in determining clinical therapy efficacy (25).

Microbiological considerations

In line with our previous study, the biological samples collected during the urological examination and during the Meares-Stamey test were immediately taken to the laboratory, under refrigerated conditions, and analyzed for cultures (11). Microbiological culture was carried out in accordance with the methods described by *Motrich* (26) and *Mazzoli* (27).

Assignment to the groups

Patients with CBP and without regard for age, or medical history were randomly allocated to receive either one tablet of levofloxacin (500 mg o.d. orally) for 14 days in association with a tablet of PROSTADEP PLUS® in the morning and a sachet of ZACHELASE® in the evening (Group A); or one tablet of levofloxacin (500 mg o.d. orally) for 14 days alone (Group B). The randomization was performed in agreement with our previous studies (28-30). Briefly we used a computer program to generate a sequence of treatment allocations by block randomization using a random number generator. Investigators were blinded to the block size to avoid selection bias.

The study design is displayed in Figure 1. We used a treatment course of 14 days to reduce the development of adverse effects related to a long course of treatment (19). The adverse events were evaluated in agreement with the common terminology criteria for adverse events (CTCAE) guidelines. Safety assessments included treatment-emergent adverse events (TEAEs) and serious AEs (SAEs).

Composition and characterization of the extracts used

PROSTADEP PLUS®

Each tablet contains SABAMAX® [*Serenoa repens* 600 (537 mg), Selenium L-methionine 55 mcg and Lycopene (*Solanum lycopersicum L.*) 4 mg].

ZACHELASE®

Each sachet contains *bromelain* (500 mg; 1.250 units), *methylsulfonylmethane* 900 mg and ascorbid acid 500 mg.

End points

The first end-point was the rate of microbiological cure and the improvement in questionnaire results recorded during the follow-up (T2-T0; T1-T0). We considered that a treatment have a clinical efficacy when a patient is asymptomatic for at least 2 weeks after the end of the treatment. Clinical failure was defined as the persistence of clinical symptoms after treatment or the suspension of therapy for significant reported adverse effects. In addition, spontaneously reported adverse events or those noted by the investigator were recorded during the whole study period.

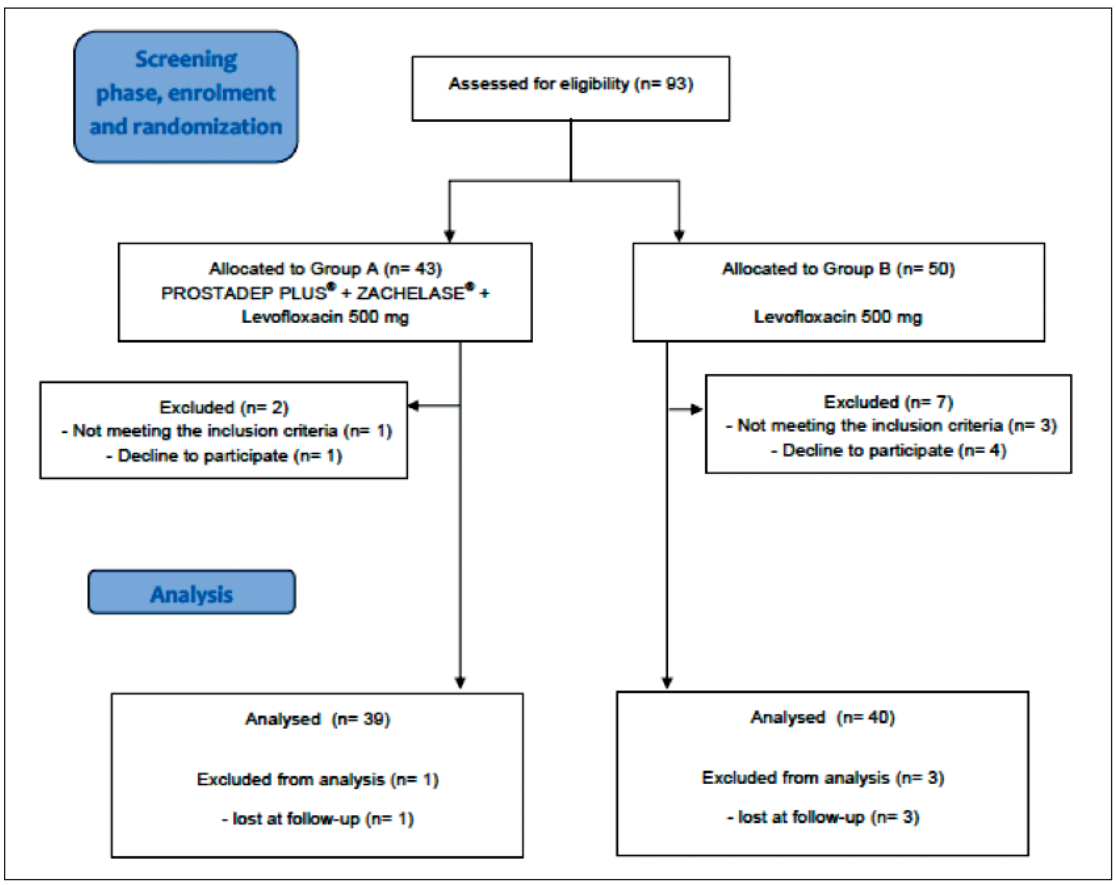


Figure 2. *The figure shows the study flow-chart in line with the CONSORT guidelines.*

Statistical analysis

The required sample size for the present study was calculated under the following conditions: Difference between the groups, 2 ± 1 score points in the NIH-CPSI pain domain; α error level, 0.05 two-sided; statistical power, 80%; and anticipated effect size, Cohen's d = 0.5. The calculation yielded 2 × 39 individuals per group. At baseline, the independent sample 2-tailed t-test was used to compare variables. For categorical parameters, chi-square test was applied.

Changes from baseline to end of therapy were analyzed using ranked one-way analysis of variance (ANOVA) with a term for treatment group. All data are expressed as mean ± standard deviation (SD). The threshold of statistical significance was set at $p < 0.05$.

All reported p-values are two-sided. All statistical analyses were performed by using SPSS 21.0 (*IBM Corporation, Armonk, NY, USA*), while G*Power (*Institut für Experimentelle Psychologie, Heinrich Heine Universität, Dusseldorf, Germany*) was used for power calculation.

Results

Patients

During the study period, 83 patients were enrolled and randomized in two groups: 40 in the group A and 43 in the group B. One patient in Group A and 3 in Group B were lost during the follow-up. Finally, 39 patients in group A and 40 patients in group B completed the study protocol (mean age 34.8 ± 5.11 years). The flow chart of this study is presented in Figure 2.

Baseline characteristics

History, clinical and questionnaires data at the time of admission are reported in Table 1. We did not record any difference in terms of symptoms or bacterial strains prevalence between the two groups.

Follow-up examination

During the first follow-up (T1), we recorded a significant difference in terms of NIH-CPSI and IPSS in the Group A (mean difference: 17.6 ± 2.65; 12.2 ± 2.33; $p < 0.01$; $p < 0.05$, respectively) and versus Group B at the intergroup analysis (mean difference: -9 ± 1.82; -8.33 ± 1.71; $p < 0.05$; $p < 0.05$, respectively) (Table 2). No differences were reported in terms of microbiological cure between the two groups. During the second follow-up (T2), questionnaire results demonstrated statistically significant differences between groups (all $p < 0.001$). One patient in Group A (2.5%) and 7 in Group B (17.9%) showed a microbiologically demonstrated symptomatic recurrence ($p = 0.02$). Significant differences were found at the intergroup analysis when we consider the outcome measures and the QoL (Figure 3).

Adverse events

All subjects correctly took the treatments showing a 100% of adherence to the treatment a 100% of compliance to the experimental protocol. Two patients, 1 (2.5%) in Group A and 1 in Group B (2.6%) developed mild adverse effects (nausea) that did not require drug discontinuation or other treatments.

Table 1.
Clinical, instrumental and laboratory patient's data at the enrolment time.

	Group A mean (SD* or %)	Group B mean (SD* or %)
Patients (n°)	39	40
Age	34.1 ± 4.58	35.0 ± 5.67
Marital Status		
married	15 (38.4)	16 (40.0)
unmarried	24 (61.6)	24 (60.0)
Educational qualification		
Primary school	-	-
High school	29 (74.3)	28 (70.0)
University	10 (25.7)	12 (30.0)
Smooking		
Yes	27 (69.2)	30 (75.0)
No	12 (30.8)	10 (25.0)
Sexually active (past month)	39 (100)	40 (100)
Sexual behaviour		
1 partner	38 (97.5)	38 (95.0)
> 1 partners	1 (2.5)	2 (5.0)
Contraceptive use		
Condom	29 (74.3)	32 (80.0)
Coitus interruptus	10 (25.7)	8 (20.0)
Start of CP# history (months)	21.3 ± 6.21	20.8 ± 7.01
Symptoms score at baseline (mean) (range)		
NIH-CPSI§	19.94 ± 2.1	19.75 ± 3.9
IPSS†	17.35 ± 3.4	18.65 ± 3.1
QoL†	0.55 ± 0.15	0.56 ± 0.18
Clinical presentation		
Dysuria	21 (53.9)	21 (52.5)
Urgency	2 (5.1)	3 (7.5)
Dysuria + frequency	4 (10.2)	5 (12.5)
Burning	12 (30.8)	11 (27.5)
Microbiological results		
E. coli	22 (56.4)	24 (60.0)
Enterococcus facealis	11 (28.2)	4 (20.0)
Other uropathogens	6 (15.4)	8 (20.0)

The table shows all anamnestic, clinical and questionnaires data at enrolment. SD*: Standard Deviation; CP#: chronic prostatitis; NIH-CPSI§: NIH Chronic Prostatitis Symptom Index; IPSS†: International Prostatic Symptom Score; QoL‡: Quality of Well-Being.

Table 2.
Questionnaire results at the first follow-up visit.

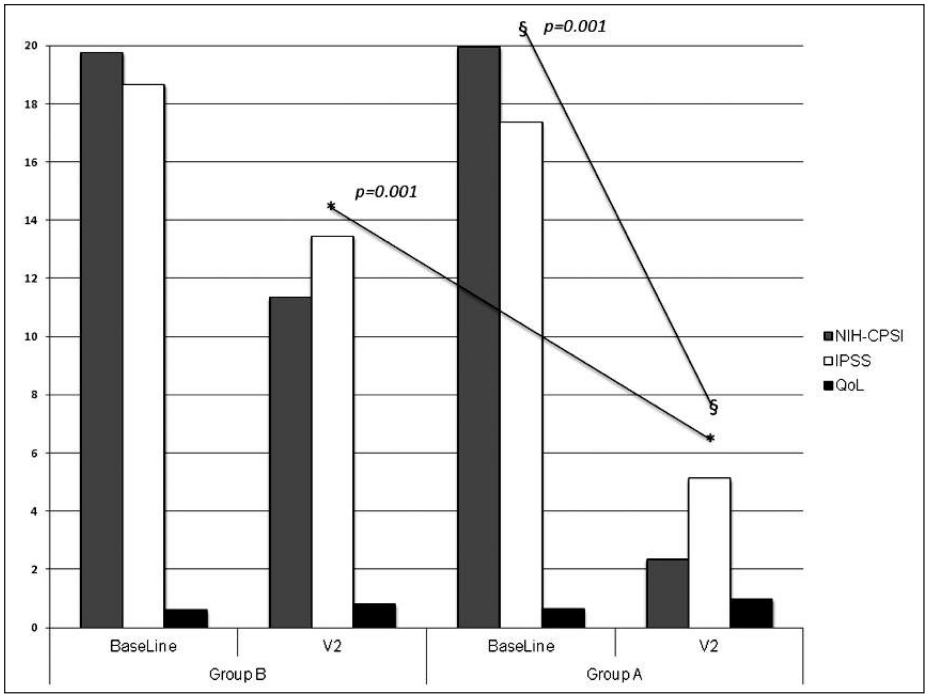
	Group A difference from baseline (SD* or %)	Group B difference from baseline (SD* or %)
Efficacy outcomes		
NIH-CPSI°	17.6 ± 2.65	8.4 ± 3.1
Treatment difference	-9 ± 1.82	
IPSS#	12.2 ± 2.33	5.2 ± 2.52
Treatment difference	-8.33 ± 1.71	
QoL§	0.31 ± 0.10	0.14 ± 0.15
Treatment difference	0.17 ± 0.03	

The table shows the mean change differences from baseline to 6 months relative to main outcome measures. NIH-CPSI§: NIH Chronic Prostatitis Symptom Index; IPSS†: International Prostatic Symptom Score; QoL†: Quality of Well-Being.

Discussion

Even if CBP has an important impact on patient's quality of life, a highly satisfactory treatment in terms of efficacy and safety still needs. CBP continues to pose a treatment challenge for all urologists and for these reasons, a lot of non-standardized treatment schedule, sometimes in off-

Figure 3.
*The figure shows the differences in terms of questionnaires results (§ NIH-CPSI; * IPSS) between the two groups. V2: visit at the second follow-up (6 months).*



label way, were offered to the patients. Here, we demonstrated that the use of combination of *Serenoa repens*, *selenium*, *lycopene* (PROSTADEP PLUS®) and *bromelain*, *methylsulfonylmethane* (ZACHELASE®) extracts is able to improve the clinical efficacy of levofloxacin in patients affected by CBP, by improving their level of quality of life. Moreover, we demonstrated a high level of treatment compliancethat may be related with the low frequency of adverse events and with the improvement of QoL. The improvement in QoL should be due to the anti-inflammatory effect of bromealin and *methylsulfonylmethane* extracts (16-17). Several Authors have demonstrated the anti-inflammtory effects of these compounds, especially in patients with severe symptoms. It is probably due to the effect of *methylsulfonylmethane* in IL-6 reduction, as demonstrated in other pathological conditions (17-18). The effect of *Serenoa repens* of prostate tissue can contribute to improve the patient's QoL and relief the pain. Several Authors demonstrated that *Serenoa repens* shows a potent anti-inflammatory properties in the whole prostate tissue (31) and is able to inhibit MCP-1/CCL2 and VCAM-1 expression by human prostate and vascular cells in an inflammatory environment, modulating the inflammatory response (32).
However, our results are probably due to synergic efficacy of all compounds, in fact it has been well documented that quinolones have antibiotic as well as immunemodulatory effects and are able to decrease the production of pro-inflammatory cytokines (15).
In this concern it is not easy to evaluate the efficacy of each single compound on the QoL improvement in CBP patients.
Finally, we believe that the phytotherapy could be an interesting multimodal approach to CBP patients due to the fact that several extracts are able to inhibit many inflammatory pathways involved in the complex pathogenesis of the disease.
However, even if our results are encouraging, this study shows some limitations, particularly the shot time of observation. In fact, it is very important to highlight that the safety of phytotherapy should be evaluated with a long-term follow-up, in order to discover delayed adverse side effects.
The use of a short-term antibiotic treatment period (14 days) should not be considered a limitation of the study because we had choice this time in agreement with the paper of *Bjerklund Johansen et al.*, that documented the minimum duration of antibiotic treatment should be 2-4 weeks (33).

Conclusion

In our study, we demonstrated that combination of *Serenoa repens*, *selenium*, *lycopene* (PROSTADEP PLUS®) and *bromelain*, *methylsulfonylmethane* (ZACHELASE®) extracts is able to improve the clinical efficacy of levofloxacin in patients affected by chronic bacterial prostatitis, without the development of adverse drug reactions.

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Contributions

TC, DT, data collecting and analyzing; TC, LG, PV manuscript writing; GM, RB, AP, VM supervision.

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