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Serenoa repens associated with *Urtica dioica* (ProstaMEV®) and curcumin and quercitin (FlogMEV®) extracts are able to improve the efficacy of prulifloxacin in bacterial prostatitis patients: results from a prospective randomised study

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ABSTRACT

We report the results of a prospective randomised study to evaluate the therapeutic effect of *Serenoa repens*, *Urtica dioica* (ProstaMEV®), quercitin and curcumin (FlogMEV®) extracts associated with prulifloxacin in patients affected by chronic bacterial prostatitis (CBP). From a whole population of 284 patients, 143 patients affected by CBP [National Institutes of Health (NIH) class II prostatitis] were enrolled. All patients received prulifloxacin 600 mg daily for 14 days, in accordance with antibiogram results. Patients were split into two groups: Group A received prulifloxacin associated with ProstaMEV® and FlogMEV®; Group B received only antibiotic therapy. Microbiological and clinical efficacies were tested by two follow-up visits at 1 month and 6 months, respectively. Quality of life (QoL) was measured using the NIH Chronic Prostatitis Symptom Index (CPSI) and International Prostatic Symptom Score (IPSS) questionnaires. Group A comprised 106 patients and Group B comprised 37 patients. One month after treatment, 89.6% of patients who had received prulifloxacin associated with ProstaMEV® and FlogMEV® did not report any symptoms related to CBP, whilst only 27% of patients who received antibiotic therapy alone were recurrence-free ($P < 0.0001$). Significant differences were found between groups in terms of symptoms and QoL ($P < 0.0001$ for both). Six months after treatment, no patients in Group A had recurrence of disease whilst two patients in Group B did. Questionnaire results demonstrated statistically significant differences between groups (all $P < 0.001$). The association of *S. repens*, *U. dioica* (ProstaMEV®), quercitin and curcumin (FlogMEV®) extracts is able to improve the clinical efficacy of prulifloxacin in patients affected by CBP.

1. Introduction

It is well known that the primary bacteria involved in the pathogenesis of chronic bacterial prostatitis (CBP) [National Institutes of Health (NIH) category II] are Gram-negative uropathogens such as *Escherichia coli* [1], although some authors have reported an emergent prevalence of Gram-positives, atypicals or anaerobes [2–4]. Although antibiotic treatment is the gold standard therapy for CBP [5], not all patients can be cured by antibiotic therapy alone [6]. Therefore, the treatment of CBP is difficult, mostly because only low-molecular-weight, lipid-soluble drugs, which are not closely linked to plasma proteins, are able to spread across the epithelial membrane [7,8]. Consequently, long-term and high-dose systemic antibiotic treatment and careful monitoring to ensure bacterial eradication is required [9]. However, long-term use of antibiotic treatment is associated with the development of many adverse effects such as gastrointestinal problems and the emergence of bacterial resistance [9]. In addition, the main object in the management of patients affected by CBP should be not only bacterial eradication [10] but also relief of symptoms [11], with a subsequent improvement in quality of life (QoL). Use of phytotherapy to alleviate symptoms related to CBP is increasing nowadays for several reasons, such as typically low side-effect profiles and costs [12], a high level of acceptance by patients [13] and, unfortunately, a high rate of inefficacy of standard treatments with subsequent patient and physician disappointment [14]. However, the use of phytotherapy in CBP is still controversial owing to several disadvantages and lack of clinical trials performed to demonstrate the safety and benefits of phytotherapy [15]. Nevertheless, even if prolonged antibiotics remain the mainstay of therapy for CBP patients [15], phytotherapy could have an adjuvant role in the management of this kind of patient by improving antibiotic efficacy or reducing related

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symptoms. Several phytotherapeutic compounds have recently been investigated to treat or prevent bacterial prostatitis, such as *Serenoa repens*, *Urtica dioica*, quercitin, cranberry, Cernilton [15–17] or other compounds such as curcumin [14,18]. We focused our attention on quercitin, curcumin, *S. repens* and *U. dioica*. Quercetin is a polyphenolic bioflavonoid with antioxidant and anti-inflammatory properties that inhibits some pro-inflammatory cytokines involved in the pathogenesis of chronic prostatitis, such as interleukin-8 and demonstrates good results in chronic prostatitis patients [16]. Moreover, *S. repens* is the most commonly used phytochemical for lower urinary tract symptom (LUTS) relief but there have been no published studies on CBP [5]. However, combination therapy with antibiotics and *S. repens* has been used in everyday clinical urological practice to eradicate infecting organisms in CBP [11]. Finally, *U. dioica* appears to be involved in antiproliferative effects by its activity on sex hormone binding globulin, aromatase, epidermal growth factor and prostate steroid membrane receptors. In addition to this antiproliferative effect, *U. dioica* appears to be an immunomodulatory agent able to improve antibiotic efficacy. However, the efficacy of *U. dioica* remains to be established in further studies [19]. Finally, as suggested by Shoskes [16], it is important that the phytotherapeutic approaches be evaluated in prospective, randomised, placebo-controlled trials with defined entry criteria and validated endpoints. The principal aim of the present study was to evaluate the efficacy of *S. repens*, *U. dioica* (ProstaMEV®), curcumin and quercitin (FlogMEV®) to improve the efficacy of prulifloxacin in patients with CBP using a randomised, prospective, long-term follow-up study.

2. Materials and methods

2.1. Study design

To evaluate the efficacy of *S. repens*, *U. dioica* (ProstaMEV®), curcumin and quercitin (FlogMEV®) to improve the efficacy of a 14-day course of prulifloxacin in CBP treatment, all consecutive patients attending the same sexually transmitted diseases (STD) centre between September 2007 and June 2008 for symptoms related to CBP and post-prostate massage (VB3) urine culture positive for uropathogens were eligible for this study.

2.2. Inclusion and exclusion criteria

Inclusion criteria were the presence of symptoms related to CBP for at least 3 months, according to the European Association of Urology (EAU) guidelines [20], 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 $\geq 10^3$ colony-forming units (CFU)/mL of uropathogens [21]. Subjects <18 years and >45 years of age, affected by major concomitant diseases, with known anatomical abnormalities of the urinary tract or with evidence of other urological diseases were excluded. Men with allergy to fluoroquinolones, who had recently (<4 weeks) undergone oral or parenteral treatment or who were currently using prophylactic antibiotic drugs were also excluded. All patients positive to tests for *Chlamydia trachomatis*, *Ureaplasma urealiticum*, *Neisseria gonorrhoeae*, herpes simplex viruses (HSV 1/2) and human papillomavirus (HPV) were also excluded. The following bacteria were considered as uropathogens, in accordance with Trinchieri [22]: enteric Gram-negative rods; enterococci, *Staphylococcus saprophyticus*; and group B streptococci. All subjects with urinary culture positive for multiple pathogens or for a pathogen known to be resistant to fluoroquinolones were excluded. Written informed consent was obtained from all patients before treatment.

2.3. Study and treatment schedule

On arrival at the STD centre, all eligible individuals signed written informed consent and underwent a baseline questionnaire, urological examination with anamnestic interview and Meares–Stamey test performed by the same urologist in accordance with the procedure described in EAU guidelines [20]. All patients who met the inclusion criteria underwent oral administration of prulifloxacin 600 mg once daily. Patients were randomised at a ratio of 3:1 to the following two groups: Group A, antibiotic therapy associated with *S. repens* (160 mg), *U. dioica* (120 mg) (ProstaMEV®), quercitin (100 mg) and curcumin (200 mg) (FlogMEV®) extracts; and Group B, antibiotic therapy alone. All patients underwent therapy for 14 days. A treatment course of 14 days was used to decrease adverse effects related to a long course of treatment with fluoroquinolones [9,23]. All patients were contacted by telephone on Day 14 of therapy to determine the correct timing and dose of treatment. Each subject was scheduled for follow-up examinations at 1 month and 6 months from the start of therapy. At each follow-up examination, a urological visit was carried out and questionnaires were collected. Patients with clinical symptoms at each follow-up visit underwent the Meares–Stamey test and were treated with an alternative antibiotic depending on the organism and its susceptibility profile. No placebo run-in period was considered necessary for the treatment of those patients with urinary culture positivity. Moreover, this was not a blinded study. The main outcome measure was the clinical cure rate at the end of the whole study period. Clinical efficacy was considered as being asymptomatic for at least 2 weeks. 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.

2.4. Composition and characterisation of extracts used

All patients assigned to Group A received oral administration of ProstaMEV® and FlogMEV® once daily.

2.4.1. ProstaMEV®

Each tablet contains 160 mg of standardised dry liposterolic *S. repens* extract (30% fatty acids and sterols) lipophilic ingredients extracted with lipophile solvents (hexane or ethanol 90%, v/v) and 120 mg of *U. dioica* dry extract extracted with lipophile solvent (0.4% β-sitosterol) (manufacturer no. 4897643, batch no. 256371).

2.4.2. FlogMEV®

Each tablet contains 200 mg of dry curcuma radix, curcumin (*Curcuma longa* L.) extract (95%) and 100 mg of dry extract of quercetin (manufacturer no. 4893644, batch no. 788284).

All compound analyses were carried out in agreement with Fiamegos et al. [24].

2.5. Sample collection and laboratory procedures

All samples were collected during the urological examination and were immediately taken to the laboratory, under refrigerated conditions, and analysed for cultures. An aliquot was taken for DNA extraction and polymerase chain reaction (PCR) for *C. trachomatis*, *N. gonorrhoeae*, HSV 1/2 and HPV detection. All subjects included in the study underwent urinary culture for common bacteria, yeasts and urogenital mycoplasma. Microbiological culture was carried out in accordance with the methods described by Motrich et al. [25]. DNA extraction and purification from urine was performed using a DNeasy1 Tissue Kit (QIAGEN S.p.A, Milan, Italy), as described in a previous study [26]. The *C. trachomatis* chromosomal DNA PCR

procedure amplifying an *omp1* gene sequence was performed on 10 mL of the sample extraction mixture according to the procedure described in a previous study [26]. This STD laboratory is registered for the UK National External Quality Assessment (NEQUAS) for microbiology for the molecular detection of *C. trachomatis* (Quality Assurance Laboratory, Health Protection Agency Centre for Infection, London, UK). The presence of both genital herpes viruses was investigated in the urine of the whole population of patients by Alpha Watch HSV 1/2 (Alphagenics Diaco Biotechnology, Trieste, Italy) and HSV 1/2 Genotype TechPlate (Diatech, Trieste, Italy). The presence of genital HPV was investigated in urine by Alpha Watch HPV (Alphagenics Diaco Biotechnology).

2.6. Questionnaires and urological examinations

The validated Italian versions of the NIH Chronic Prostatitis Symptom Index (NIH-CPSI) [27] and the International Prostatic Symptom Score (IPSS) [28] were administered to each patient. The questionnaire was self-administered when the patient arrived at the STD centre.

2.7. Statistical analysis

A two-tailed *t*-test for independent samples was used to compare QoL by clinical outcome. The χ^2 test was used to evaluate the relationship between the QoL questionnaire and other parameters. Fisher's exact test was also used to assess the significance of other statistical analyses. The Mann–Whitney test was also performed to compare QoL mean values at different follow-up examinations and other parameters. Statistical significance was achieved if the *P*-value was <0.05. All reported *P*-values are two-sided. All data were recorded, collected and analysed using SPSS 11.0 for Apple-Macintosh (SPSS Inc., Chicago, IL).

3. Results

From a whole population of 284 subjects attending the STD centre for symptoms related to CBP and VB3 urine positive for uropathogens, 206 patients were considered for enrolment in the study. However, 52 subjects were excluded for positivity to *C. trachomatis*. In addition, 11 patients were excluded because they were lost at follow-up. In total, 143 men (mean age 31.7 ± 7.09 years) were enrolled. All the randomised groups had comparable distributions in terms of all tested clinical and laboratory parameters.

3.1. Clinical presentation and microbiological results

All clinical and laboratory characteristics at the time of enrolment are described in Table 1. The present results confirm the emerging prevalence of Gram-positive strains in patients affected by CBP, with a ratio of 1.6 between Gram-positive and Gram-negative strains. All patients reported a mean symptom time of 21.20 months (range 12–31 months). The mean times according to groups are displayed in Table 1. The baseline questionnaire mean scores were 19.94 ± 4.41 and 17.53 ± 2.74 for NIH-CPSI and IPSS, respectively. Questionnaire data results at baseline evaluation according to groups are displayed in Table 1. No differences were reported between patients with symptoms for ≥24 months and those with symptoms for <24 months in terms of NIH-CPSI (0.27) and IPSS (0.85) mean scores.

3.2. Clinical evaluations at the first follow-up

At the first follow-up examination (1 month after treatment), 95 (89.6%) of 106 patients in Group A did not report symptoms related to CBP compared with 10 (27.0%) of 37 patients in Group B [statistically significant difference ($P < 0.0001$) between the two groups]. Among the 11 patients in Group A with recurrence after treatment, 9 presented VB3 urine cultures positive for *E. coli* and 2 for both *E. coli* and *Enterococcus faecalis* and underwent alternative antibiotic therapy according to their susceptibility profile (pathogens were resistant to prulifloxacin). In Group B, 15 of 27 patients with recurrence presented VB3 urine cultures positive for both *E. coli* and *E. faecalis* and 12 for both *E. coli* and *Enterobacter* spp. and underwent alternative antibiotic therapy according to their susceptibility profile (pathogens were resistant to prulifloxacin). The questionnaire results after 1 month of treatment were as follows: Group A, NIH-CPSI 1.96 ± 2.20, IPSS 5.36 ± 2.58; and Group B, NIH-CPSI 11.02 ± 5.88, IPSS 12.24 ± 4.27. Statistically significant differences were reported between the groups ($P < 0.0001$ for both).

Table 1
Clinical and laboratory characteristics of patient at enrolment ($N = 143$).

	Group A	Group B
No. of patients	106	37
Median age (±S.D.) (years)	30.8 (5.60)	31.9 (6.19)
Sexually active (past month)	106 (100)	37 (100)
Sexual behaviour		
1 partner	52 (49.1)	20 (54.1)
>1 partner	54 (50.9)	17 (45.9)
Contraceptive methods		
No contraceptive methods	48 (45.3)	14 (37.8)
Condom	49 (46.2)	13 (35.1)
Coitus interruptus	9 (8.5)	10 (27.0)
Spermicide	–	–
Clinical data		
Clinical presentation		
Urinary symptoms	103 (97.2)	37 (100)
Burning	68 (66.0)	24 (64.9)
Tenesmus	22 (21.4)	13 (35.1)
Painful micturition	74 (71.8)	33 (89.2)
Dysuria + frequency	49 (47.6)	34 (91.9)
Urgency	29 (28.2)	9 (24.3)
Pain	40 (37.7)	27 (73.0)
Perineal	16 (40.0)	8 (29.6)
Scrotal	2 (5.0)	–
Suprapubic	12 (30.0)	12 (44.4)
Lower abdominal	10 (25.0)	7 (25.9)
Start of CBP history (months)	20.71 ± 5.05	22.62 ± 6.19
Symptoms score at baseline (±S.D.)		
NIH-CPSI	19.67 ± 4.71	20.70 ± 3.35
IPSS	17.37 ± 2.58	17.97 ± 3.15
Laboratory data		
Positive Meares–Stamey test	106 (100)	37 (100)
Gram-positive bacteria	69 (65.1)	19 (51.4)
Enterococcus spp.	62 (89.9)	12 (63.2)
Streptococcus B group	12 (17.4)	6 (31.6)
Staphylococcus saprophyticus	18 (26.1)	9 (47.4)
Gram-negative bacteria	37 (34.9)	18 (48.6)
Escherichia coli	33 (89.2)	16 (88.9)
Klebsiella spp.	6 (16.2)	3 (16.7)
Proteus mirabilis	1 (2.7)	2 (11.1)
Serratia spp.	8 (21.6)	5 (27.8)
Enterobacter spp.	10 (27.0)	12 (66.7)

S.D., standard deviation; CBP, chronic bacterial prostatitis; NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; IPSS, International Prostatic Symptom Score.

3.3. Clinical evaluations at the second follow-up

At the end of follow-up examination (6 months), 96 (90.6%) of 106 patients in Group A were recurrent disease free, whilst in

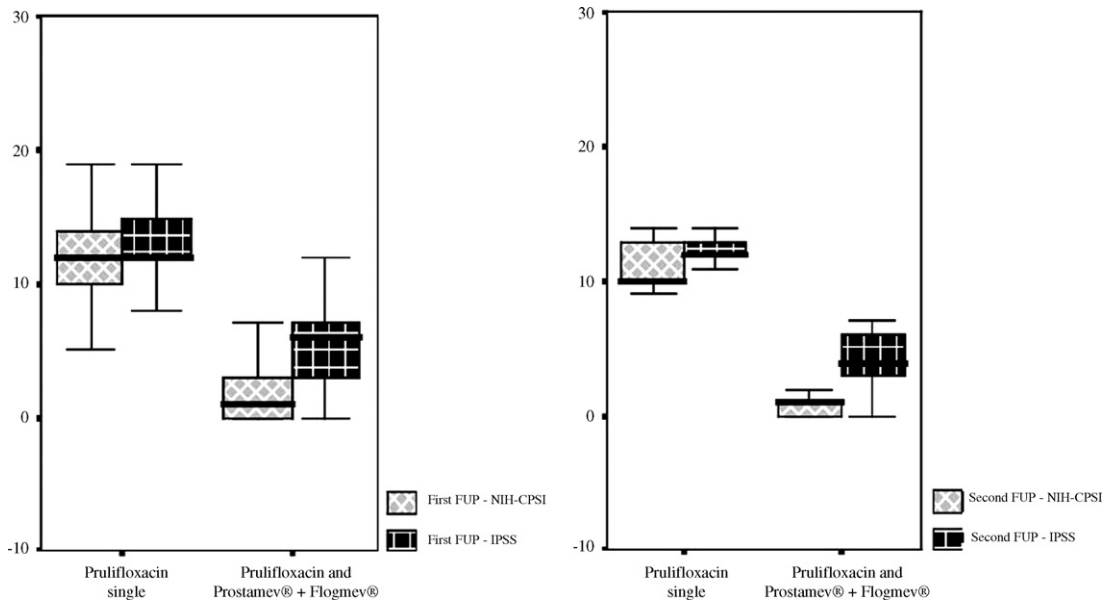

Fig. 1. Mean questionnaire results according to treatment groups and different follow-up (FUP) examinations. NIH-CPSI, National Institutes of Health Chronic Prostatitis Symptom Index; IPSS, International Prostatic Symptom Score.

Group B only 8 (21.6%) of 37 patients did not report any symptoms. Two patients in Group B who were disease-free at the first follow-up evaluation demonstrated recurrence at 5 months and 6 months after treatment. The questionnaire results after 6 months from treatment were as follows: Group A, NIH-CPSI 1.35 ± 1.75, IPSS 4.63 ± 2.29; and Group B, NIH-CPSI 10.51 ± 3.72, IPSS 11.72 ± 3.98. Statistically significant differences were demonstrated between the groups ($P < 0.0001$ for both). The mean questionnaire results according to the groups and different follow-up examinations are displayed in Fig. 1.

No differences were reported between patients with symptoms for ≥24 months and patients with symptoms for <24 months in terms of NIH-CPSI (0.27) and IPSS (0.85) mean scores according to the different follow-up examinations.

3.4. Adherence to treatment schedule and adverse effects

All patients correctly took all 14 doses of prulifloxacin associated or not with other compounds, showing compliance with the study protocol of 100%. Only 3 patients (2.8%) in Group A and 1 patient (2.7%) in Group B had mild adverse effects that did not require treatment suspension.

4. Discussion

Chronic prostatitis continues to pose a treatment challenge for all urologists. In CBP the goal of treatment is not only the eradication of the infecting organisms but also recurrence prevention [10,11]. Therefore, although the prevalence of CBP (NIH category II) is low [29], patients reported a poor QoL due to the frequent recurrence of disease [11]. The major aim in CBP patient management is therefore prevention of bacterial relapse. However, consecutive repeated cycles of antibiotic therapy are never able to prevent bacteria relapsing and, consequently, improve QoL [30]. This study was designed to assess the efficacy of a schedule of prulifloxacin associated with phytotherapeutic agents such as *S. repens*, *U. dioica* (ProstaMEV®), curcumin and quercitin (FlogMEV®) in comparison with a schedule of prulifloxacin only to improve CBP patient QoL and to prolong the recurrence-free time after treatment. The present schedule did not present any patient drop-out and is therefore safe and shows good patient compliance. Use of *S. repens*, *U. dioica*, curcumin and quercitin extracts associated with prulifloxacin leads to good results in terms of QoL and prolonged recurrence-free time. The improvement in QoL should be due to the anti-inflammatory effect of quercitin extract. Several studies have demonstrated an anti-inflammatory effect in vitro owing to an increase in antioxidant capacity [31]. The good results obtained in QoL improvement could be due to the fact that the quercitin supplements have a greater effect in patients with increased levels of inflammation and oxidative stress [32]. The decrease in symptoms could also be due to the anti-inflammatory effects shown by curcumin that have been demonstrated in several clinical trials, probably due to the inhibition of a number of different molecules that play a role in inflammation [32]. Recently, it has been established that the anti-inflammatory effect of curcumin is most likely mediated through its ability to inhibit cyclooxygenase-2, lipoxygenase and inducible nitric oxide synthase [33]. The other extract administered to patients was *U. dioica*, which showed an inhibitory effect on NF-κB activation [34]. The fact that *U. dioica* can mediate an anti-inflammatory effect by different pathways from curcumin and quercitin may be the biological reason for the clinical effect. Another point to take into consideration is the fact that quinolones showed an anti-inflammatory effect in association with the antibiotic effect [6]. Our study is the first study aiming to evaluate the clinical effect of an association of several phytoextracts to improve the clinical benefit of a therapy based on prulifloxacin in CBP patients. Among the extracts of natural origin, we included *S. repens*. This compound has been used in clinical urological practice in the management of LUTS due to benign prostatic enlargement and chronic abacterial prostatitis [34]. Only one study has been performed to evaluate the effects of *S. repens* associated with quinolones in the management of CBP, but the authors used repeated cycles and α-blockers in addition to the therapy [11]. The innovation of this schedule is the fact that the patients were not subjected to α-blockers without collateral effects and with a stable relief of symptoms. In addition, we believe that phytotherapy for CBP should consist of several extracts in order to inhibit many inflammatory pathways involved in the pathogenesis of the disease. Finally, another key point to discuss is the important and emergent prevalence of Gram-positive strains in patients affected by CBP, as described by several authors [2,35]. The change in the bacterial population isolated from CBP patients should be taken into account in planning the therapy schedule.

Furthermore, the fact that some pathogens became resistant to prulifloxacin during the treatment period is probably due to the short treatment period used. However, no indication regarding the correct prulifloxacin treatment period in patients affected by CBP has been reported in the literature. Nevertheless, in accordance with Bjerklund Johansen et al. [36], who stated that the minimum duration of antibiotic treatment should be 2–4 weeks, we decided to use a 14-day treatment course. The association between antibiotic drugs and phytotherapeutic agents such as *S. repens*, *U. dioica* (ProstaMEV®), quercitin and curcumin (FlogMEV®) extracts is able to improve the clinical efficacy of prulifloxacin in patients affected by CBP.

Moreover, this therapeutic schedule is able to achieve more stable and long-standing results in terms of QoL. In addition, the results of this study should be considered in order to take into account the fact that QoL is the main target in chronic prostatitis patient management. The present study shows a few limitations. No placebo arm was included. However, the possible biases caused by the lack of a placebo arm were considered in the results analysis. Moreover, owing to the fact that a mixture of phytotherapeutics was used, the attributing effect of each phytotherapeutic cannot be evaluated. Finally, the fact that this is not a blinded study should be a limitation of the study, however future blinded studies should confirm these findings.

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