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# Symptoms and quality of life in HIV-infected patients with benign prostatic hyperplasia are improved by the consumption of a newly developed whole tomato-based food supplement. A phase II prospective, randomized double-blinded, placebo-controlled study

Eugenia Quiros-Roldan, MD, PhD [a], Canio Carriero, MD [a], Simone Paghera, BSc [b], Melania Degli Antoni, MD [a], Chiara Fiorini, BSc [b], Virginia Quaresima, PhD [b], Francesco Castelli, MD [a], Luisa Imberti, MD [b,*]

[a] Department of Infectious and Tropical Diseases, University of Brescia and ASST Spedali Civili di Brescia, Italy
[b] Centro di Ricerca Emato-oncologica AIL (CREA), Diagnostic Department, ASST Spedali Civili di Brescia, Italy

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ABSTRACT

Carotenoid rich diets have proven to be beneficial in decreasing urinary symptoms of benign prostatic hyperplasia (BHP) and cardiovascular risk factors, especially following the consumption of whole tomato, the major source of dietary lycopene. Here, we describe the results of a phase II prospective, randomized double-blinded, placebo-controlled study undertaken to determine the efficacy and safety of a novel whole tomato-based food supplement (WTFS) containing lycopene in highly bioavailable form in 31 HIV+ patients with proved BPH. The consecutive enrolled patients received daily, for 12 weeks, 5 g of WTFS or placebo.

The study demonstrates that WTFS consumption is associated with a statistically significant improvement of all BPH symptoms and quality of life, free/total prostate specific antigen ratio, and diastolic blood pressure, with a trend in interleukin 6 level reduction.

WTFS may offer a side effect-free food supplement for the management of BPH in HIV+ patients.

## 1. Introduction

A rapidly accumulating and overwhelming amount of evidences suggests that a diet containing high quantitative of lycopene, a carotenoid present in tomato and in some other vegetables and fruits, results in a lower risk for several types of cancer, cardiovascular and metabolic diseases (Cheng et al., 2017, Heber & Lu, 2002, Imran et al., 2020, Mazidi et al., 2020, Saini et al., 2020, van Breemen & Pajkovic, 2008). In addition, a favorable effect of tomato and lycopene intake on total and cause-specific mortality has recently described (Mazidi, Katsiki, George, & Banach, 2020), while a low circulating lycopene concentration has been proposed as one of the first signs of low-grade inflammation that it is involved in the onset and progression of many diseases (van Steenwijk, Bast, & de Boer, 2020).

Most of epidemiological evidences linking lycopene uptake and cancer incidence are focused on prostate cancer risk (Bowen et al., 2002, Chen et al., 2001, Giovannucci et al., 1995, Mirahmadi et al., 2020, Schwarz et al., 2008, van Breemen et al., 2011, Zu et al., 2014) because this carotenoid improves intracellular metabolism and reduces proliferation of normal and cancerous prostate epithelial cells, DNA damage, and local androgen signaling (Ilic & Misso, 2012, Obermüller-Jevic et al., 2003, Wertz, Siler, & Goralczyk, 2004). In this context,

*Abbreviations:* BPH, benign prostatic hyperplasia; HDL, high-density lipoprotein; interleukin, IL-6; IPSS, International Prostate Symptom Score; LDL, low-density lipoprotein; LUTS, low urinary tract symptoms; PSA, prostate specific antigen; T0, before WTFS initiation; T1, after 12-week consumption of WTFS; WTFS, whole tomato-based food supplement.

* Corresponding author at: Centro di Ricerca Emato-oncologica AIL (CREA), Diagnostic Department, ASST Spedali Civili di Brescia, Piazzale Spedali civili, 1 25123 Brescia, Italy.

*E-mail addresses:* eugeniaquiros@yahoo.it (E. Quiros-Roldan), canio.carriero@teletu.it (C. Carriero), simonepaghera@gmail.com (S. Paghera), m.degliantoni@unibs.it (M. Degli Antoni), chiara.fiorini.18@gmail.com (C. Fiorini), quaresima.virginia@gmail.com (V. Quaresima), francesco.castelli@unibs.it (F. Castelli), luisa.imberti@asst-spedalicivili.it (L. Imberti).

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phytocompounds in the form of plant portions or extracts have been used in the treatment of prostate diseases (Pagano, Laudato, Griffo, & Capasso, 2014), demonstrating efficacy in controlling low urinary tract symptoms (LUTS), with no side effects and not inferiority to alpha-adrenergic blockers or 5-alpha-reductase inhibitors (Morgia et al., 2018; Smit et al., 2017). This has suggested a potential efficacy of lycopene in preventing of benign prostatic hyperplasia (BPH) or in the improvement of BPH-associated symptoms (Ilic & Misso, 2012, Wertz et al., 2004). However, the healthy properties of whole tomato preparations cannot be explained by the lycopene content alone (Canene-Adams et al., 2007, Rowles et al., 2020). Indeed, a large number of anti-inflammatory compounds and constituents, already present in small amounts or newly formed during culinary processing, have been identified in tomato extracts (Chaudhary, Sharma, Singh, & Nagpal, 2018; Mohri et al., 2008) which contribute to their final *in vivo* efficacy (Alcaraz et al., 2020, Mossine, Chopra, & Mawhinney, 2008).

Recently, a whole tomato-based food supplement (WTFS) has been developed by Janus Pharma SrL (Italy) and registered by the Italian Health Ministry (registration n. 68843, 2018–19) with the claims "antioxidant" and "prostate health". In a pilot study, this WTFS, given to symptomatic BPH patients, decreased LUTS in about 80% of the cases (Cellini et al., 2018). Another study reported that WTFS improved quality of life and induced a reduction of total prostate specific antigen (PSA) levels in BPH patients with baseline levels above 10 ng/mL (Cormio et al., 2021).

It is well known that BPH is associated with chronic inflammation (both systemic and local), traditional cardiovascular risk factors and with the presence of previous sexually transmitted diseases (Semczuk-Kaczmarek, Płatek, and Szymański, 2020, Chen, Tsai, & Tong, 2012, Langston et al., 2019), all features frequently present in human immunodeficiency virus (HIV)-infected patients (Cingolani et al., 2014, Quiros-Roldan et al., 2016, Quiros-Roldan et al., 2017). Although few data are available about BPH epidemiology and apparently no increased risk of BPH has been described in HIV-infected men (Ahlström et al., 2015), prostate cancer is projected to be one of the most common types of cancer among HIV-infected men in United States by 2030 (Shiels et al., 2018). This can be linked to the fact that antiretroviral therapy (ART), which successfully induces HIV viral suppression and greatly reduces HIV infection-associated mortality, does not normalize the underlying chronic inflammation (Quiros-Roldan et al., 2017; Quiros-Roldan et al., 2020).

To the best of our knowledge, no studies investigated the effects of lycopene supplementation on the inflammatory features of HIV-infected patients with BPH. Thus, in this study, we have investigated the efficacy of the WTFS in HIV-infected patients with BPH with focus on LUTS, PSA values and on a panel of variables related to cardiovascular risk.

## 2. Materials and methods

### 2.1. Materials

WTFS is a dietary supplement, administered as powder dissolved in water, containing whole tomato and a small percentage of olive's polyphenols. The preparation, with the composition reported in Table 1, is specially processed to make their complex of antioxidant and anti-inflammatory micronutrients, ie carotenoids, mainly lycopene and flavonoids, highly bioavailable (EU patent n. 3052113-14 772134.4; Fogliano, Iacobelli, & Piantelli, 2016).

Total lycopene content in one WTFS sachet was 23,75 mg; in particular, 9.5 mg isomers and 12.5 mg all-rans, 1.75 mg 5-cis were contained in the carotenoid fraction of the product. The calories of a single dose of WTSF are 17 (EU patent).

**Table 1**
Composition of the WTFS.

| | |
|---|---|
| *Tomato powder composition (g/ 100 g)* | |
| Proteins | 10.2 |
| Lipids | 3.4 |
| Carotenoids | 0.500 |
| Lycopene isomers | 0.190 |
| Alpha-tocopherol | 0.0023 |
| Total flavonoids | 0.200 |
| Ketosamines | 0.008 |
| Fibres | 14.9 |
| Humidity | <5 |
| *Polyphenolic content in olive extract (w/w)* | |
| Hydroxytyrosol | 10% |
| Unidentified polyphenols | 8% |
| Ligstroside dialdehyde aglycon | 7% |
| Oleuropein dialdehyde hydeaglycon | 6% |
| Verbascoside | 6% |
| Pinoresinol and deacetoxypinoresinol | 5% |
| Tyrosol | 3% |
| Ligstroside aglycon | 2% |

Placebo consisted a preparation of orange/maltodextrin powder.

### 2.2. Study design and patients

A phase II prospective, randomized double-blinded, placebo-controlled trial was conducted at the Infectious Diseases Unit of the University of Brescia and at CREA of ASST Spedali Civili of Brescia.

The study protocol was approved by the Ethical Committee of Brescia (NP #3465). Patients signed an informed consent form and clinical research was conducted in accordance with the principles for medical research involving human subjects described in the Declaration of Helsinki. Patients also consented to the publication of clinical results.

Patients were recruited from January to February 2020; the 12-week follow-up took place from March to April 2020. They met the following criteria: aged older than 18 years, HIV infection, stable antiretroviral therapy, plasmatic HIV RNA < 20 copies/mL, and BPH at rectal examination and trans rectal echography.

Exclusion criteria were: current or previous prostatic carcinoma, history of transurethral resection of the prostate, chronic/acute diseases of the urinary tract, inflammatory diseases of the urogenital tract (i.e. orchitis, epididymitis, or both), and AIDS event in the previous 3 months. In addition, patients reporting a history of hypersensitivity to tomato and malabsorption syndrome were excluded.

The patients were randomized 1:1 by one of the researchers not involved in data collection in two groups: arm A or arm B, according to the randomization number. Patients of arm A received an oral dose of WTFS (5 g) every 24 h, for 12 weeks, while those of arm B received the placebo (5 g).

The patients were recommended not to use other food supplements during the study and to follow their habitual dietary regimens. At the end of the study, after completing the statistical analysis, the researchers revealed which arm was WTFS or placebo.

Before WTFS supplementation initiation (T0) and after 12 weeks (T1), patients filled the International Prostate Symptom Score (IPSS), the only questionnaire validated by WHO available in Italian language, which consists of 7 questions (Q) regarding specific urinary symptoms associated with BPH. Each question is assigned points from 0 to 5, indicating increasing severity of a specific symptom. The total score therefore ranges from 0 to 35 (from asymptomatic to very symptomatic) and patients can be classified as follows: 0–7 = mildly symptomatic; 8–19 = moderately symptomatic; and 20–35 = severely symptomatic. Patients also underwent body measurements, including weight, height,

abdominal circumference (measured at the level of the umbilicus), body mass index, measurement of systolic and diastolic blood pressure, and heart rate. Moreover, fasting blood samples were collected at T0 and T1, and 0.5 mL of serum aliquots were immediately frozen and stored at −80 °C until processing.

Quantitation of total and free PSA as well as of IL-6 were performed using Roche Diagnostics kits.

### 2.3. Outcomes

The primary outcome was to evaluate modifications on the validated IPSS questionnaire and quality of life.

Secondary exploratory parameters were any variations on PSA, glucose, total-, high-density lipoprotein (HDL) or low-density lipoprotein (LDL), cholesterol, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma glutamyl transferase (GGT), and IL-6 levels. Clinical and laboratory parameter of HIV infection were also evaluated.

### 2.4. Statistical analysis

The results were analyzed using GraphPad Prism (version 5.1, GraphPad Software, San Diego, CA, USA). Initially, D'Agostino and Pearson omnibus normally test was applied to evaluate the normality of the data. Data were presented as mean and standard deviation (SD), unless otherwise stated. Unpaired *t* test was used to evaluate differences between arms (WTFS vs placebo) and Paired *t* test for differences between T0 and T1. Discrete quantitative data were analyzed using the Chi-square test and presented as frequency and percentage. Values of $P < 0.05$ were considered statistically significant.

## 3. Results

Thirty-one patients were enrolled in the study (Fig. 1); 16 of them were randomized to arm A and 15 to placebo. All patients successfully completed treatment with no side effects and performed T0 and T1 visits spite of COVID-19 emergency. At T0, there were no statistically significant differences regarding HIV infection characteristics between arms. Although the mean duration of HIV infection was shorter in WTFS arm, the mean age of patients was significantly higher in WTFS than in

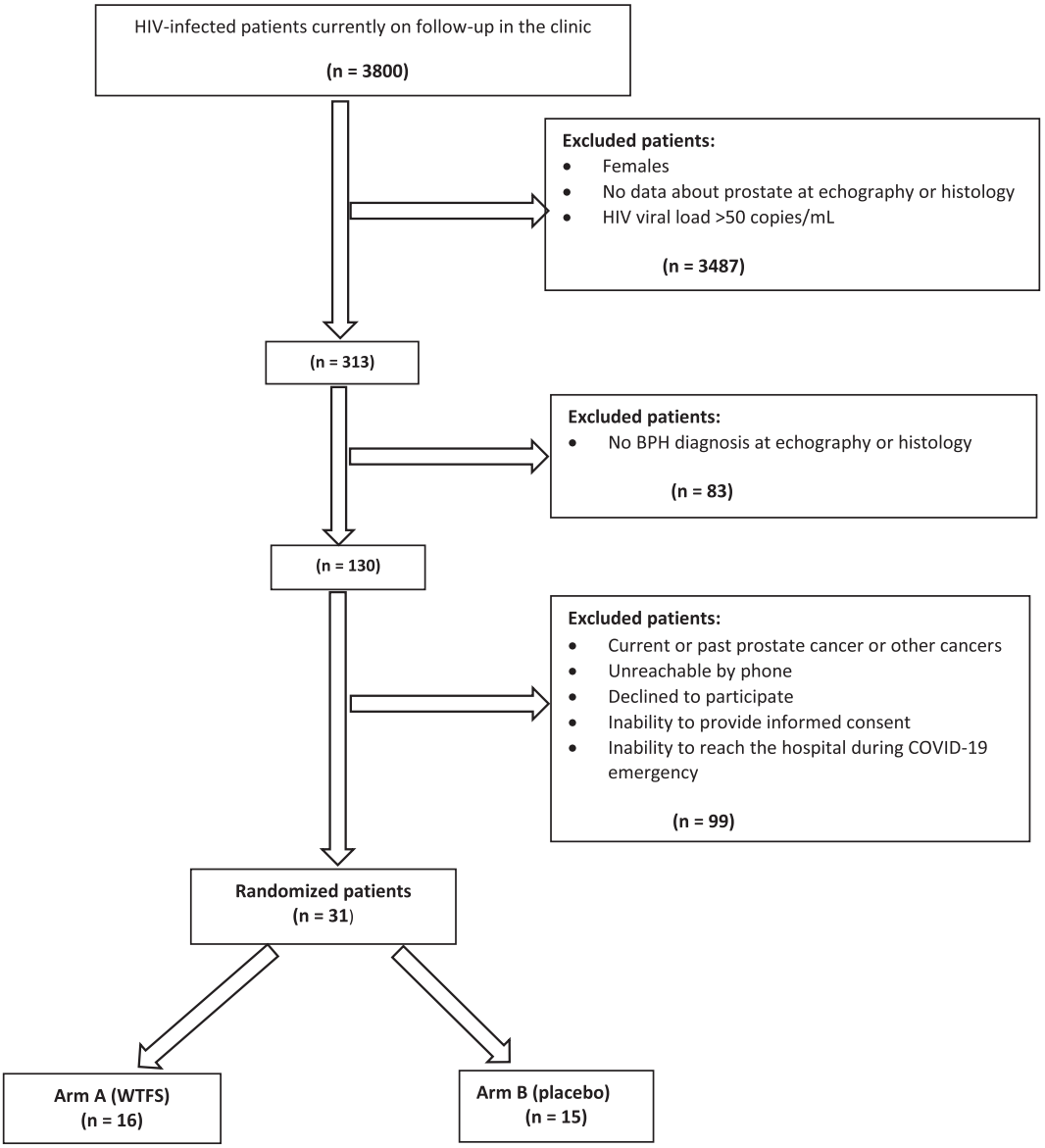


**Fig. 1.** Flow chart of HIV+ patient enrollment. BPH: benign prostatic hyperplasia, n: number, WTFS: whole tomato food supplement.

**Table 2**
Characteristics of enrolled patients.

| | WTFS | Placebo | P-value |
|---|---|---|---|
| Age, years | 69 (8) | 63 (7) | **0.0246** |
| Height, cm | 176 (7) | 174 (6) | 0.5449 |
| Years with HIV | 17 (8) | 22 (8) | 0.1015 |
| CD4 at diagnosis, cells/μL | 269 (226) | 330 (205) | 0.4329 |
| CD4 nadir, cells/μL | 159 (145) | 181 (101) | 0.6400 |
| AIDS, patients (%)* | 5 (31) | 4 (27) | 0.9085 |
| BPH[a] therapy, patients (%)* | 8 (50) | 3 (20) | 0.1710 |

[a]BPH: Benign prostatic hyperpasia. Data are shown as mean and SD, except for *. P-value were calculated by Unpaired *t* test for continues variables and by Chi-square test for discrete variables. $P < 0.05$ were considered significant and were reported in bold.

**Table 3**
Mean values of International Prostate Symptom Scores recorded at baseline (T0) and after 12 weeks (T1).

| | WTFS | | | Placebo | | |
|---|---|---|---|---|---|---|
| | T0 | T1 | P-value | T0 | T1 | P-value |
| Incomplete emptying (Q1) | 2.44 ± 0.48 | 1.06 ± 0.30 | **0.0041** | 1.73 ± 0.32 | 1.73 ± 0.32 | 1.0000 |
| Frequency (Q2) | 2.38 ± 0.33 | 1.38 ± 0.29 | **0.0127** | 1.87 ± 0.41 | 2.33 ± 0.32 | 0.0894 |
| Intermittency (Q3) | 1.69 ± 0.27 | 0.50 ± 0.20 | < **0.0001** | 2.07 ± 0.43 | 1.53 ± 0.36 | 0.0148 |
| Urgency (Q4) | 1.94 ± 0.31 | 0.88 ± 0.30 | < **0.0001** | 1.73 ± 0.30 | 1.33 ± 0.35 | 0.1383 |
| Weak Stream (Q5) | 3.63 ± 0.41 | 1.94 ± 0.28 | < **0.0001** | 2.67 ± 0.40 | 2.67 ± 0.43 | 1.0000 |
| Straining (Q6) | 1.50 ± 0.33 | 0.63 ± 0.22 | 0.0058 | 1.40 ± 0.40 | 1.40 ± 0.40 | 1.0000 |
| Nocturia (Q7) | 3.06 ± 0.39 | 1.13 ± 0.24 | < **0.0001** | 2.27 ± 0.33 | 2.07 ± 0.37 | 0.2711 |
| Quality of life | 3.44 ± 0.16 | 1.56 ± 0.26 | < **0.0001** | 3.12 ± 0.19 | 3.12 ± 0.24 | 1.0000 |

Data shown are mean ± SE. P-values were calculated by Paired *t* test. $P < 0.05$ were considered significant and were reported in bold.

placebo arm (Table 2).

Mean values of IPSS recorded at T0 and T1 are shown in Table 3.

Fig. 2 shows the effects of treatment (in percentage of changes) on the symptoms contributing to the IPSS score. In the WTFS arm, all symptoms relating to obstruction (question (Q) 1 and Q5), storage (Q2, Q4, and Q7), intermittency (Q3), and straining (Q6), significantly improved, along with the quality of life. Nocturia was the symptom with the most significant improvement score in WTFS arm (it decreased of about 40% from T0 to T1). Conversely, intermittency symptoms significantly improved during the study period in the placebo arm. Changes in IPSS score from T0 to T1 in the individual HIV+ patients are showed in Fig. 3. In the WTFS arm, the severely symptomatic score of 5 patients decreased to moderately symptomatic, and the moderately symptomatic score of 9 patients decreased to mildly symptomatic. One patient with moderately symptomatic score become asymptomatic; in one patient the score remained unchanged. In the placebo arm, only one patient showed an IPSS score decrease.

Eight patients in WTFS (patient ID 2, 6, 9, 10, 22, 25, and 29) and 3 in placebo (patient ID 7, 28, and 31) arms, were symptomatic spite were assuming a treatment with alpha-1-adrenergic antagonists or 5-alpha-reductase inhibitors for more than 6 months. The treatment with WTFS, but not with placebo, induced a clear clinical improvement, when measured by IPSS.

No significant differences in total PSA level were observed from T0 and T1 in both arms, neither in free PSA level (Table 4). However, a statistical increase of free/total PSA ratio level was observed from T0 to T1 in WTFS treated subjects with no significant variation in placebo arm.

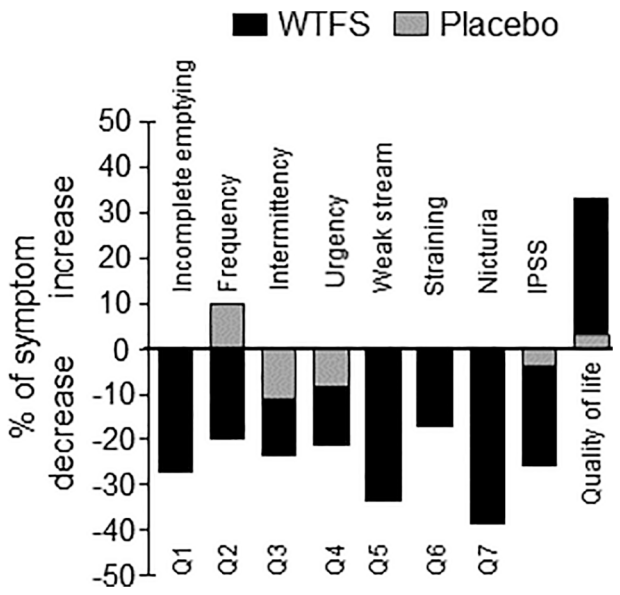


**Fig. 2.** Percentage of increase/decrease of urinary symptoms and quality of life between baseline (T0) and 12 weeks of WTFS or placebo consumption (T1) in HIV+ patients with BPH. Responses to questions (Q)1 and Q5 regard obstruction symptoms; Q2, Q4, and Q7 storage symptoms; Q3 intermittency symptoms; and Q6 straining symptoms. IPSS: International Prostate Symptom Score; WTFS: whole tomato food supplement.

Table 4 also shows variations between T0 and T1 for other variables including those related to cardiovascular risk and HIV infection follow-up.

WTFS assumption was associated with statistically significant reductions in mean diastolic blood pressure) and a trend toward a reduction of systolic blood pressure levels from T0 to T1 (- 7 mmHg for both blood pressures). Similar effects were not observed with placebo.

No significant changes overtime in fasting glucose, total-, LDL-, and HDL- cholesterol were observed between the two arms. Opposite, a trend toward IL-6 decrease in WTFS arm was observed, that was evident in the patients with highest baseline levels of IL-6 (data not shown), while in placebo arm, IL-6 serum levels increased.

The percentage of CD4 slightly decreased from T0 to T1 in WTFS arm, but their total number remained unchanged in both groups.

## 4. Discussion

Results of this double-blind, randomized, placebo-controlled, exploratory study indicate that 12-weeks assumption of WTFS by HIV+ patients with BPH is associated with a statistically significant improvement of LUTS, quality of life, free/total PSA ratio, and diastolic blood pressure, together with a trend in IL-6 level reduction. Notably, these effects are achieved with no side effects, which penalize a fraction of BPH patients treated with alfa-adrenergic blockers or 5 alfa-reductase inhibitors, the latter containing sitosterol. Furthermore, the use of WTFS overcomes the side effects of tomato consumption (Salehi et al., 2019).

A large body of epidemiologic and clinical studies are supporting the evidence that a continuous uptake of tomato-rich diets is associated in a dose-dependent manner with a lower in incidence of prostate cancer (Er et al., 2014). In this context, a recently developed WTFS, consisting of a whole tomato undergoing a controlled thermal treatment, is effective in contrasting carotenoid serum depletion (Vitaglione et al., 2007), in reducing the levels of circulating inflammatory and angiogenetic molecules and in delaying tumor progression in the mouse model of prostate carcinogenesis (TRAMP) (Pannellini et al., 2010).

Although metabolic syndrome and chronic inflammation, both considered as risk factors for BHP, are frequently observed in elderly

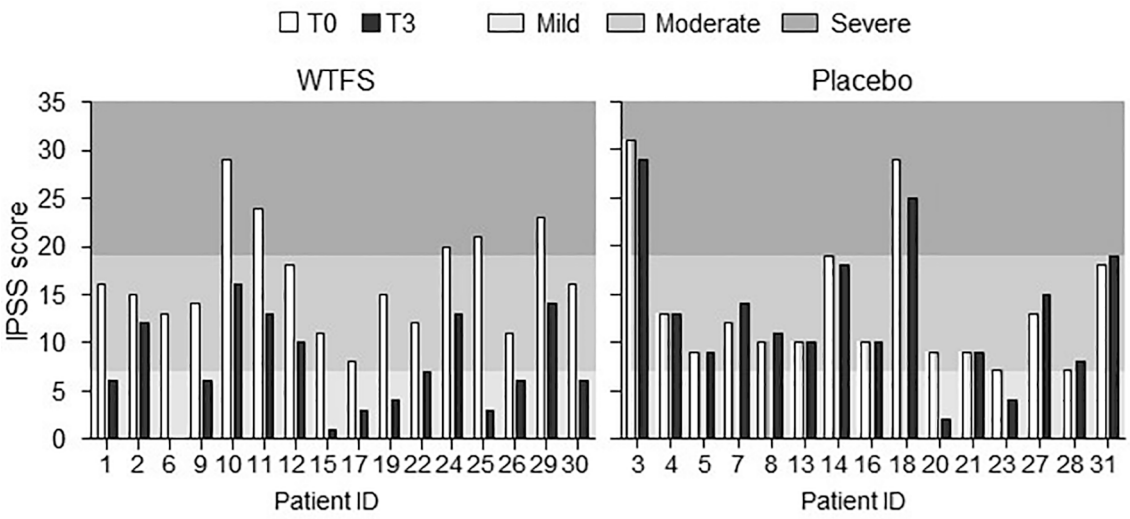


**Fig. 3.** Change of IPSS score between baseline (T0) and 12 weeks of WTFS or placebo consumption (T1) in individual HIV+ patients with BPH. IPSS: International Prostate Symptom Score; WTFS: whole tomato food supplement.

**Table 4**
Blood test values and cardiovascular-related risk factors recorded at baseline (T0) and after 12 weeks (T1).

| | WTFS | | | Placebo | | |
|---|---|---|---|---|---|---|
| | T0 | T1 | P-value | T0 | T1 | P-value |
| Weight, Kg | 82 ± 15 | 82 ± 15 | 0.6326 | 85 ± 12 | 85 ± 13 | 0.4417 |
| BMI, Kg/m$^2$ | 26.49 ± 4.40 | 26.61 ± 4.30 | 0.6333 | 28.10 ± 4.15 | 28.24 ± 4.23 | 0.4159 |
| Abdominal circumference, cm | 101 ± 11 | 101 ± 11 | 0.9280 | 104 ± 11 | 104 ± 9 | 0.8115 |
| Systolic pressure, Hgmm | 136 ± 11 | 129 ± 13 | 0.0790 | 131 ± 13 | 133 ± 12 | 0.4721 |
| Diastolic pressure, Hgmm | 85 ± 7 | 78 ± 9 | **0.0032** | 83 ± 9 | 83 ± 10 | 0.8760 |
| Heart rate, bpm | 74 ± 6 | 75 ± 7 | 0.6710 | 73 ± 7 | 74 ± 3 | 0.4988 |
| White blood cells, x10$^3$/μL | 6.2 ± 1.6 | 5.9 ± 1.2 | 0.4612 | 6.6 ± 1.6 | 6.2 ± 1.3 | 0.3947 |
| Neutrophil granulocytes, x10$^3$/μL | 3.3 ± 1.3 | 3.0 ± 0.7 | 0.1958 | 3.4 ± 1.3 | 3.2 ± 0.9 | 0.3859 |
| Lymphocytes, x10$^3$/μL | 2.1 ± 0.7 | 2.2 ± 0.6 | 0.2731 | 2.3 ± 0.6 | 2.3 ± 0.8 | 0.6860 |
| Platelets, x10$^3$/μL | 221 ± 41 | 221 ± 35 | 0.2539 | 225 ± 50 | 210 ± 46 | 0.0553 |
| Hemoglobin, g/dL | 14.8 ± 1.1 | 14.9 ± 1.3 | 0.4267 | 15.1 ± 1.1 | 14.4 ± 1.3 | 0.0993 |
| Aspartate aminotransferase, U/L | 27.13 ± 12.88 | 29.50 ± 11.61 | 0.2623 | 29.53 ± 10.87 | 32.40 ± 10.57 | 0.2177 |
| Alanine aminotransferase, U/L | 32.00 ± 24.89 | 34.63 ± 28.33 | 0.2654 | 38.20 ± 24.60 | 40.93 ± 17.93 | 0.4756 |
| Gamma glutamyl transferase, U/L | 29.31 ± 10.71 | 32.25 ± 26.39 | 0.6434 | 32.13 ± 19.46 | 34.73 ± 16.06 | 0.3045 |
| Creatinine, mg/dL | 1.22 ± 0.37 | 1.33 ± 0.31 | **0.0144** | 1.09 ± 0.14 | 1.2 ± 0.19 | **0.0014** |
| Blood glucose, mg/dL | 106.3 ± 21.4 | 108.7 ± 22.6 | 0.4414 | 105.7 ± 22.5 | 107.3 ± 18.3 | 0.5454 |
| Triglycerides, mg/dL | 129 ± 32 | 158 ± 57 | **0.0453** | 146 ± 74 | 171 ± 102 | 0.1977 |
| Total cholesterol, mg/dL | 191 ± 30 | 194 ± 32 | 0.6084 | 176 ± 41 | 189 ± 46 | 0.0986 |
| HDL-cholesterol, mg/dL | 46 ± 8 | 46 ± 6 | 0.7072 | 40 ± 7 | 41 ± 8 | 0.3801 |
| LDL-cholesterol, mg/dL | 120 ± 31 | 116 ± 33 | 0.4739 | 107 ± 41 | 114 ± 47 | 0.3301 |
| PSA[a], μg/L | 2.89 ± 2.21 | 2.75 ± 1.62 | 0.3547 | 3.15 ± 2.34 | 3.01 ± 2.01 | 0.3651 |
| PSA free[b], μg/L | 0.64 ± 0.32 | 0.83 ± 0.28 | 0.3208 | 1.10 ± 0.43 | 0.92 ± 0.40 | 0.6708 |
| PSA ratio[c], % | 17.62 ± 7.28 | 23.24 ± 8.60 | **0.0259** | 23.35 ± 6.76 | 23.50 ± 5.26 | 0.3907 |
| Interleukin-6, ng/L | 5.30 ± 4.99 | 3.56 ± 2.27 | 0.1978 | 3.79 ± 1.48 | 4.41 ± 2.28 | 0.4034 |
| CD4, cells/μL | 698.6 ± 342.3 | 686.6 ± 299.3 | 0.7144 | 807.1 ± 353.6 | 694.9 ± 255.7 | 0.0938 |
| CD4, % | 30.3 ± 9.7 | 28.5 ± 9.4 | **0.0167** | 29.3 ± 6.6 | 27.8 ± 6.4 | 0.0992 |
| CD8, cells/μL | 957.7 ± 466.7 | 1009 ± 431.3 | 0.4000 | 892.1 ± 276.1 | 920.5 ± 389.7 | 0.6495 |
| CD8, % | 41.5 ± 11.5 | 41.4 ± 11.5 | 0.9074 | 36.8 ± 9.9 | 37.3 ± 10.8 | 0.3461 |
| CD4/CD8, ratio | 0.9 ± 0.7 | 0.8 ± 0.6 | 0.0521 | 0.9 ± 0.5 | 0.9 ± 0.5 | 0.1736 |

Data shown are mean ± (SD). P-value was calculated by Paired *t* test; P < 0.05 were considered significant and were in bold in the Table.
[a] PSA: prostate specific antigen.
[b] free PSA was determined if total PSA was above 2 μg/L.
[c] Free PSA / Total PSA.

HIV-infected patients (Bloch, John, Smith, Rasmussen, & Wright, 2020), no studies have evaluated the effects of lycopene or lycopene-containing food supplements in these patients. Because the effect of lycopene is likely to be largely due to the anti-inflammatory properties of the tomato micronutrients (Zhao et al., 2020), we have challenged the results of this pilot study by investigating the effect of the WTFS in patients with chronic inflammation such HIV+ patients with BPH. Actually, although only few information is available, HIV+ patients are not described to have an increased incidence of BPH (Ahlström et al., 2015), which is not considered a pre-malignant lesion (Roehrborn & McConnell, 2002). However, a long-term, large cohort study, has demonstrated that clinical BPH is associated with a significant increased risk of prostate cancer incidence (Ørsted, Bojesen, Nielsen, & Nordestgaard, 2011), which is expected to increase in HIV+ patients in the near future (Shiels et al., 2018).

In a very recent work, performed on patients with BPH not infected with HIV, the assumption of WTFS for 2 months induced a reduction of PSA levels in those patients with values above 10 ng/mL (Cormio et al.,

2021). We could not appreciate this effect because none of our patients had PSA levels above 10 ng/mL (Cormio et al., 2021). On the contrary, although it is not correct to compare values from two different studies due to possible biases (different practitioners, study periods, and length of treatment), the symptoms contributing to the IPSS score at the pre-treatment were apparently more evident in our patients than those of uninfected individuals (Cormio et al., 2021), and the IPSS improvement was more manifest than in non-infected individuals. This is not surprising, since the higher levels of inflammation present in HIV+ patients may result in an increase in IPSS. Indeed, a recent systematic review reports that low circulating lycopene concentrations correlate with higher inflammation biomarkers in patients with various diseases in the general population (van Steenwijk et al., 2020). In particular, HIV infection is associated with high concentrations of several markers of systemic inflammation, including the pro-inflammatory cytokine IL-6, soluble monocyte activation markers, such as sCD14 and sCD163, and lipopolysaccharide even among those with undetectable HIV replication (Sereti et al., 2017, Burdo et al., 2011). Interestingly, IL-6 has been found to be a stronger predictor of all-cause mortality risks and nonfatal clinical events in HIV-infected patients than C-reactive protein or D-dimer (Borges et al., 2016). However, although the WTFS consumption results into a significant improvement of LUTS and quality of life, only a trend in decrease of circulating IL-6 levels has been observed in our study in HIV+ patients with PBH. This is not surprising since lycopene uptake displays a high level of variability among individuals (Marques, Reis Lima, Oliveira, & Teixeira-Lemos, 2015) and because the carotenoid, by concentrating in the reproductive system, can achieve locally an anti-inflammatory effect which is unlikely to be seen in blood (Marques, Reis Lima, Oliveira, & Teixeira-Lemos, 2015). The possibility that WFTS may play a role in suppressing production of IL-6 in HIV-infected patients will probably require more studies with higher WTFS dosage and/or for prolonged times. In this regard, being lycopene a safe molecule (Substances Generally Recognized as Safe GRAS - Docket No.: FDA-1997-N-0020) ver, the prolonged use of WTFS is unlikely to result in the appearance of side effects.

The WTFS production method, not only generates more bioavailable *cis*-lycopene and increased tomato phenolic components, but also produces Fru-His compounds that further increase tomato health-preserving properties (Mossine et al., 2008). Thus, this supplement is likely to possess a spectrum of mechanisms which can concur in delaying the onset or decrease the severity of a number of co-morbidities reported in HIV+ patients, such as metabolic syndrome, type 2 diabetes, or a wide range of cardiovascular diseases (Bloch et al., 2020).

BPH and LUTS are frequent in men aged over 50 years and they may not only be a consequence of prostate enlargement, but also of several complex mechanisms. Nitric oxide/cyclic guanosine monophosphate (NO/cGMP) signaling pathway, metabolic syndrome and chronic inflammation could be associated with the severity and progression of the disease (Gacci et al., 2013; Mouli & McVary, 2009; Nickel, Roehrborn, Castro-Santamaria, Freedland, & Moreira, 2016; Russo et al., 2018). Interestingly, patients with BPH and chronic inflammation, not only have a higher risk of disease progression, but also show lower response to medical therapy (Mishra et al., 2007, Tuncel et al., 2005). Medicinal plants, in the form of plant parts or extracts, are commonly used for the treatment of prostatic diseases, such as prostatitis and BPH, and for prevention of prostate cancer (Cicero et al., 2019). Accordingly, patients with BPH showed IPSS improvement after 8–12 weeks of supplementation with several herbal preparation (Coulson et al., 2013, Russo et al., 2016). For instance, a daily consumption of tomato products, containing 30 mg lycopene for 3 weeks, apparently reduces total PSA value in patients with intermediate risk of prostate cancer (Paur et al., 2017). In our cohort of HIV-infected patients with BPH we did not observe a significant variation in total PSA, but we found a free/total PSA ratio increase.

Regarding the other biological effects of lycopene, it is known that lycopene may reduce lipids by inhibiting 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA)-reductase (Silaste, Alfthan, Aro, Kesäniemi, & Hörkkö, 2007) and by enhancing LDL degradation. In a recent randomized clinical trial, 15 days of tomato product consumption significantly enhanced the protection of lipoproteins from oxidative stress (Fuhrman, Partoush, Volkova, & Aviram, 2008). Although we have not found statistically significant differences on lipids profile, a trend in LDL decrease was observed only in the WTFS arm, spite of known effect of the lockdown during COVID pandemic on eating habits and lifestyle behaviors (Cheikh Ismail et al., 2020, Hadley, Clinton, & Schwartz, 2003).

It has also been reported that lycopene supplementation reduces blood pressure. This effect is probably mediated by the inhibition of the angiotensin converting enzyme (ACE) and by antioxidant effects, that may reduce the oxidative stress induced by angiotensin-II, and by indirectly enhancing production of nitric oxide in the endothelium (Cancello, Soranna, Zambra, Zambon, & Invitti, 2020, John, Ziebland, Yudkin, Roe, & Neil, 2002, Mazidi, Katsiki, George, & Banach, 2020; Mozos et al., 2018, Saini et al., 2020). In our study, we observed a decrease (−7 mmHg) in both diastolic and systolic blood pressure. However, evidence for the effects of lycopene supplementation on oxidative stress is scarce and more studies are necessary to prove this possibility.

Finally, in our study, WTFS improved LUTS in HIV+ patients pharmacologically treated for BPH. A similar feature was described in patients, without HIV infection, treated with *Serenoa repens*, lycopene and selenium plus tamsulosin, who achieved a greater reduction in the IPSS and in post-voiding urinary volume than those treated with tamsulosin alone (Morgia et al., 2018).

These evidences could dispel the doubts that still persist about the efficacy of phytotherapic compounds for PBH treatment (Grammatikopoulou et al., 2020).

The strength of the study is its double-blind, randomized, placebo-controlled design, but it also has several limitations. First, it was performed during COVID-19 Italian lockdown, and it may have been a confounding factor for dietary habits (diet was not monitored). In addition, lycopene blood concentration was not measured. Finally, no calculation of the sample size was performed, and this may limit, at least in part, the robustness of the results.

Therefore, further clinical studies on a larger sample cohort with the addition of more objective outcomes such as flow rate, prostate histology or size variation are required.

## 5. Conclusions

This study adds further evidence that the newly developed WFTS is clinically relevant in the management of BPH with no associated side effects also in HIV-infected patients.

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## Author Contributions

QRE and IL conceived the study. QRE and CC made substantial contributions to the acquisition of clinical data. CF and QV performed laboratory tests. PS performed statistical analysis. IL and QRE wrote the first version of the manuscript. All authors revised critically for important intellectual content. All authors read and approved the final manuscript.

## Ethics statement

The study protocol was approved by the Ethical Committee of Brescia (NP #3465). Patients signed an informed consent form and

clinical research was conducted in accordance with the principles for medical research involving human subjects described in the Declaration of Helsinki.

## Author contribution

**Eugenia Quiros-Roldan:** Conceptualization, Methodology, Investigation, Writing - original draft. **Canio Carriero:** Investigation, Data curation. **Simone Paghera:** Data curation. **Melania Degli Antoni:** Formal analysis. **Chiara Fiorini:** Methodology. **Virginia Quaresima:** Methodology, Writing - review & editing, Experiments. **Francesco Castelli:** Validation. **Luisa Imberti:** Conceptualization, Supervision, Project administration, Methodology, Writing - original draft, Writing - review & editing.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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