Improvement of Urinary Tract Symptoms and Quality of Life in Benign Prostate Hyperplasia Patients, Associated with Consumption of a Newly Developed whole Tomato Based Food Supplement. A phase II prospective, Randomized Double-blinded, Placebo-controlled Study.

Luigi Cormio  
Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences

Beppe Calò  
Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences

Manuela Iezzi  
Department of Medicine and Aging Sciences, Center for Advanced Studies and Technology (CAST),

Alessia Lamolinara  
Department of Medicine and Aging Sciences, Center for Advanced Studies and Technology (CAST),

Paola Vitaglione  
Department of Agricultural Sciences, University of Naples, Portici

Giovanni Silecchia  
Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia

Giuseppe Carrieri  
Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia

Vincenzo Fogliano  
Department of Agrotechnology and Food Sciences

Stefano Iacobelli  
Janus Pharma Srl

Pier Giorgio Natali  
Department of Medicine and Aging Sciences, Center for Advanced Studies and Technology (CAST)  
https://orcid.org/0000-0002-2843-3313

Mauro Piantelli  
Department of Medicine and Aging Sciences, Center for Advanced Studies and Technology (CAST)
Keywords: Benign prostate hyperplasia, lower urinary tract symptoms, tomato, olive polyphenols, food supplement.

DOI: https://doi.org/10.21203/rs.3.rs-66796/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License. Read Full License
Abstract

**Background:** Benign prostatic hyperplasia is the most common urologic disease among elderly men. The diagnosis of BPH is usually in response to the appearance of lower urinary tract obstructive, and post-micturition symptoms (LUTS) that can significantly affect the quality of life. In

Aim of this study was to evaluate in a phase II prospective, randomized double-blinded, placebo-controlled study, the efficacy and safety of a novel whole tomato-based food supplement on LUTS of patients affected by benign prostatic hyperplasia.

**Methods:** Thirty-four consecutive patients with histologically proved BPH were included in a phase II prospective, randomized double-blinded, placebo-controlled study. Patients were randomized to receive daily for two months a sachet (5 grams) of the tomato-based food supplement Lycoprozen® or an identical sachet containing placebo. Patients were asked to fill the “International Prostatic Symptom Score” questionnaire before and after treatment.

**Results:** All patients successfully completed the scheduled regimen. No side effects were recorded. Lycoprozen® significantly reduced the LUTS severity. Particularly, the IPSS mean values before and after the treatment were 7.5±1.1 SE (range 16-2) and 5.1±1.0 SD (range 14-2), respectively (paired t-test, two-tailed p value <0.0002). A trend toward a reduction of total PSA levels was observed in Lycoprozen® treated patients (9.346 ng/ml±1.839 SE vs. 7.906±0.928 SE, P = 0.096) (Fig 1, left). This trend was sustained by the significant reduction of PSA levels seen in 5 patients, (2 obese, 2 over-weight and 1 normal-weight) with basal levels >10 ng/ml (18.520ng/ml±2.747 SE vs. 10.323ng/ml±2.073 SE, P = 0.009)

**Background**

Benign prostatic hyperplasia (BPH) affects aging men and is the most common urologic disease among elderly men [1]. BPH is the consequence of the proliferation of both epithelial and stromal cells from the transition zone and periurethral prostatic areas. It typically develops after the age of 40 years, ranging in prevalence from >50% at 60 years to as high as 90% by 85 years [2].

The diagnosis of BPH is frequently in response to the appearance of lower urinary tract obstructive, and post-micturition symptoms (LUTS), i.e. urinary hesitancy, urgency, frequency and post void dribble. Pharmacological treatment possibilities include α-adrenergic antagonists or 5-α reductase inhibitors, however one-third of patients with LUTS do not respond to either treatment approach [3] and a fraction of responder are penalized by the occurrence of side-effects. Patients who are resistant to medical treatment, or who become resistant to treatment over time will become candidates for surgical intervention to reduce LUTS severity.

Further understanding the causes of LUTS will guide interventions to prevent LUTS or increase sensitivity to medical treatment. To date, there are multiple theories on the cellular and molecular processes
underlying the pathogenesis of BPH leading to a symptomatic disease. In addition to androgens, both chronic and acute inflammation can lead to events that can cause proliferation within prostatic tissue through a variety of mechanisms, notably oxidative stress [4, 5]. At present, non-steroidal anti-inflammatory drugs are used to improve urinary symptoms and flow measures, but their long-term effectiveness and safety are not known [6].

BPH is also associated with obesity and related pathologies. However, the biological pathways linking obesity and BPH are poorly understood. Centralized adipose deposition was associated with the severity of prostate tissue inflammation and LUTS and an approach to minimize centralized fat deposition may reduce LUTS severity in BPH patients [7].

A large number of anti-inflammatory compounds has been identified in tomato extracts [8, 9]; moreover, tomato consumption reduces inflammation by decreasing inflammatory cytokines in overweight and obese men [10, 11].

Also, we have observed that a diet enriched with a 10% whole tomato [12] versus a tomato-free control diet increased the anti-oxidant serum activity and to reduce serum levels of inflammatory biomarkers in the TRAMP mouse model of prostate carcinogenesis, even before the appearance of cancer [13]. As a result, a decrease in cancer incidence and in mortality was observed. The role of lycopene is relevant, as lycopene poor whole tomato food supplement failed to duplicate these findings [14]. However, the antineoplastic activity of the whole tomato preparations cannot be explained by the lycopene content alone [15–17], and constituents already present in small amounts or newly formed during processing also contribute to their final in vivo efficacy [18].

Recently, a novel food supplement named Lycoprozen® was developed by Janus Pharma, Rome, Italy and commercialized according to the Italian Ministry of Health (2018-19). The registered indications were: “antioxidant” and “prostate health”. Lycoprozen® consists of whole tomato specially processed for make their complex of antioxidant and anti-inflammatory micronutrients highly bioavailable, with the addition of a small percentage of olive’s polyphenols [19].

In a pilot study, we observed that Lycoprozen®, at the dosage of one sachet/day for two months, decreased LUTS symptoms in about 80% of the BPH patients [20]. To further confirm this finding, in the present study, we have tested Lycoprozen® in a phase II prospective, randomized double-blinded, placebo-controlled study, in patients with histology proven BPH.

**Materials, Methods And Patients**

The food supplement Lycoprozen® (Italian Health Ministry registration n. 68843) is produced by a patented solvents-free process [19] resulting into an increased bioavailability of antioxidant and anti-inflammatory tomato micronutrients, which include carotenoids (mainly lycopene in increased cis-configuration), flavonoids, and ketosamines. Lycoprozen® tomato and olive vegetation water compositions are reported in Table 1 and Table 2, respectively.
Thirty-four consecutive patients having undergone prostate biopsy (PBx) at our Institution and having been diagnosed with benign prostate hypertrophy were included in a phase II prospective, randomized double-blinded, placebo-controlled study. Indications for trans-rectal ultrasound guided PBx were increased serum Prostate Specific Antigen (PSA) (≥ 4 ng/mL) and/or abnormal digital rectal examination. The inflammation present in prostatic biopsies was assessed and graded according to the Irani’s score for both the histologic inflammation grading (extension of inflammatory cells, range 0–3) and aggressiveness (the effect of inflammatory cells on prostate tissue, range 0–3) [21]. All Lycoprozen® prostate biopsies from treated subjects showed inflammation ranging from grade 1 to grade 3.
Patients reporting a history of hypersensitivity to tomato, inflammatory diseases of the urogenital tract (i.e. orchitis, epididymitis or both) and malabsorption syndrome were excluded. All patients were from the same regional district of Puglia in south Italy and their dietary habits were overall reflecting the use of a Mediterranean Diet. Patients were randomized into two Groups: Group A received one oral sachet of Lycoprozen® (5 grams) every 24 hours, for two months while Group B received the placebo. Placebo consisted of orange/maltodextrin.

Patients sera were collected before and after the treatment, then frozen and stored at -80°C. Quantitation of total and free PSA as well as of cytokines/growth factors (IL-1, IL-6, IL-8, IL-17, IL-18, Angiopoietin 2, VEGF A) in these samples were performed by a multiplex assay (Milliplex®, Merk Life Science, Milano, Italy).

During the study all participants avoided the use of other questionnaire before and after the treatments. The main outcome measures were a reduction of LUTS and improved quality of life at the end of the study period. Data were evaluated by paired t-test, two-tailed.

The study protocol was approved by the University of Foggia Ethics Committee (Nov.8, 2017, registration number 871-16) and was carried out in agreement with the provisions of the Declaration of Helsinki. Written informed consent was obtained from all patients.

Results

The characteristics of Lycoprozen® treated patients (Group A) were not significantly different from those of placebo assuming subjects (Group B), in terms of age, prostate volume, prostate inflammation and serum PSA levels (Table 3).

| Patients baseline characteristics | Group A | Group B | P value |
|----------------------------------|---------|---------|---------|
| Age                              | 63.4±3.0| 62.9±3.0| 0.320   |
| Prostate volume (ml)             | 55.2±6.9| 60.0±7.8| 0.300   |
| Prostate flogosis (IRANI score)  | 2.3±0.3 | 1.75±0.3| 0.146   |
| Total PSA (ng/mL)                | 9.3±1.8 | 6.3±1.2 | 0.168   |

All patients successfully completed treatment with no side effect. No patient reported significant changes in their body mass. The International Prostatic Symptoms Score (IPSS) is based on the answer to seven questions concerning urinary symptoms, and is the only questionnaire validated by WHO in Italian language. Each question is assigned points from 0 to 5, indicating increasing severity of a particular 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; 20-35 = severely symptomatic. In our series of 10 mildly and 7 moderately affected patients, we have found that Lycoprozen® significantly reduced the LUTS severity. The IPSS mean values before and after the treatment were $7.5 \pm 1.1$ SE (range 16-2) and $5.1 \pm 1.0$ SD (range 14-2), respectively (paired t-test, two-tailed p value <0.0002).

The treatment was significantly effective in reducing IPSS score in both mildly ($4.60 \pm 0.75$ SE vs $3.10 \pm 0.43$, P=0.012) and moderately symptomatic patients ($12.17 \pm 1.01$ SE vs $10.17 \pm 1.17$, P=0.007).

The effects of treatment on the symptoms contributing to the IPSS score are detailed in Table IV. In particular, Lycoprozen® strongly reduced both urination frequency (P = 0.001) and urgency (P < 0.0001). As a consequence, a significant improvement of life quality was referred by Lycoprozen® assuming patients (P = 0.0002) (Table 4). IPSS score and quality of life were not affected by placebo treatment (data not shown).

### Table 4
**Effects of Lycoprozen® treatment on IPSS symptoms.**

| Symptoms:          | Pre-treatment score | Post-treatment score | P value  |
|--------------------|---------------------|----------------------|----------|
| 1 Incomplete emptying | 1.50±0.29           | 1.63±0.27            | P = 0.164 |
| 2 Frequency        | 1.00±0.16           | 0.13±0.50            | P = 0.001 |
| 3 Intermittency    | 1.38±0.26           | 1.44±0.26            | P = 0.334 |
| 4 Urgency          | 0.81±0.14           | 0.00±0.00            | P < 0.0001 |
| 5 Weak Stream      | 1.38±0.26           | 1.69±0.30            | P = 0.555 |
| 6 Straining        | 1.00±0.26           | 0.94±0.27            | P = 0.867 |
| 7 Nicturia         | 0.44±0.13           | 0.06±0.06            | P = 0.013 |
| Quality of life    | 2.19±0.40           | 1.38±0.33            | P = 0.0002 |

A trend toward a reduction of total PSA levels was observed in Lycoprozen® treated subjects ($9.346 \pm 1.839$ SE vs $7.906 \pm 0.928$, P = 0.096) (Fig. 1, left). Actually, this trend was sustained by the significant reduction of PSA concentrations seen in the five patients, (2 obese, 2 over- and 1 normal-weight), with basal levels $>10$ ng/ml ($18.520 \pm 2.747$ SE vs. $10.323 \pm 2.073$, P = 0.009) (Fig. 1, right). On the other hand, at the end of the observation period, a trend toward an increase of total PSA was seen in placebo treated subject ($6.284 \pm 1.199$ SE vs $7.123 \pm 1.095$, P = 0.080).

Free PSA concentrations were not modified by the treatment (data not shown). In addition, free/total PSA ratios were similar before and after the Lycoprozen® treatment ($18.81 \pm 3.34$ SE vs $20.38 \pm 3.15$, P =
0.663), and this is also true in the case of overweight/obese patients (27.60±8.23 SE vs 23.40±4.61 SE, 

Discussion

Lycoprozen® is a mixture of whole tomato powder and a polyphenolic extract from olives. The original tomato powder was firstly used to produce a food for special medical purposes (FSMP) and investigated as an adjuvant therapy in subjects affected by chronic hepatitis C. This FSMP was effective in preventing carotenoid serum depletion and improving the oxidative status during antiviral therapy [12]. Then, the anti-tumoral activity of the tomato powder was evaluated in a transgenic mouse model of prostate carcinogenesis (TRAMP) [13]. In this model, treating mice with the tomato powder significantly delayed tumor progression and decreased both the incidence of poorly differentiated carcinoma and mortality. Additionally, in agreement to several other reports, tomato supplementation was found to reduce the levels of circulating inflammatory/angiogenic cytokines as IL-6, VEGF and TNF alpha. IL-6 in a number of experimental models [23-25]. The patented method to produce Lycoprozen® leads to a final product enriched in bio-active compounds, i.e. olive's polyphenols which have been found more active than the tomato powder alone in reducing serum levels of IL-6 and VEGF in TRAMP mice [19]. Serum measurement of a panel of inflammatory cytokines in the pretreatment sera did not show any significant derangement (data not shown). This does not come unexpected since the prostate inflammation in BPH patients is unlikely to be mirrored in circulation.

Chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS) is a urinary disorder that afflict patients due to various discomforts. It is pressing and meaningful to develop novel and effective treatments because of the uncertain etiology and dismal therapeutic effect of CP/CPPS. In the absence of a standard treatment [26], the use of substances like antioxidants that may stop or potentially reverse the deleterious effects of inflammation is particularly attractive. Tomatoes and olives are the source of complexes of micronutrients endowed with well-known strong antioxidants and anti-inflammatory activity, with properties potentially useful in protecting DNA and other cell constituents from oxidation [27, 28].

Here we demonstrate that Lycoprozen® determines a significant improvement of urinary tract symptoms and quality of life in BPH patients, thus representing a suitable alternative option to the pharmacological treatment of this age-related pathology. Although the molecular mechanisms underlying this clinical benefit remains to be investigated, in a rat model lycopene was found to attenuate chronic prostatitis/chronic pelvic pain syndrome by inhibiting oxidative stress and inflammation via the interaction of NF-κB, MAPKs, and Nrf2 signaling pathways [29].

Indeed, in addition to lycopene, tomatoes contain within their matrix other bioactive compounds which are responsible of the health effects associated with a constant consumption of the fruit, which cannot be accounted solely by lycopene [17, 30]. The patented of Lycoprozen® production method, in fact, not only generates more bioavailable cis-lycopene and increased tomato phenolic components, but produces frus-his compounds which further increase tomatoes health preserving properties [18]. Thus
Lycoprozen® is likely to possess a spectrum of cooperative mechanisms. In view that the increase of the epithelial and stromal components in BPH are not clearly paralleled by noticeable proliferation, the hyperplastic lesions have been interpreted as the result of impaired programmed cell death mechanism [31, 32]. In this regard tomato sauce has been reported to increased apoptosis in different experimental models [33, 34]. Stromal cells are responsible for the androgen mediated glandular epithelium growth. Although a defined molecular pathway has not been yet defined, tomato and lycopene have been reported to down-regulate androgen metabolism and signaling [35].

Inflammation is a common histopathological finding in BPH, in absence of prostatic cancer or clinical prostatitis. It is a condition of which subclinical inflammation may be associated with a raise of serum PSA levels [36]. However weak is the correlation between PSA levels and the active or chronic inflammation and no significant correlation exists between the active or chronic histopathological inflammation and IPSS [37]. Also, in this regard nutritional interventions with tomato-products reduced PSA levels in subgroups of prostate patients, while lycopene supplements or extracts were found to be less effective [38-41].

In addition, the mix of polyphenols from tomatoes and from olive vegetation water, can certainly contribute to the anti-inflammatory properties of Lycoprozen [42, 43].

Lycoprozen® can modulate the total PSA concentrations even in patients with BPH. We have observed an increasing total PSA trend in the placebo group (P=0.080), probably as the consequence of the bioptic procedure. Indeed, cystoscopy can increase serum PSA levels fourfold, while needle biopsies and transurethral resection can temporarily increase PSA levels up to fiftyfold, all as a result of increased PSA leakage into the serum. In addition, the relatively long half-life of PSA may lead to a consistent delay before serum PSA returns to a baseline level after TURP, biopsy, or infection [44]. On the contrary, a trend toward a reduction of total PSA levels was observed in Lycoprozen® treated patients (P=0.096), which was sustained by the significant reduction of total PSA concentrations seen in the patients with high basal levels (>10 ng/ml; P = 0.009).

Although BPH and prostate cancer (PCa) share features such as hormone-dependent growth and response to treatment with anti-androgen therapy, BPH is not considered a premalignant lesion. However, in a nationwide cohort study involving more than 3 million men followed for up to 27 yr, clinical BPH was associated with a two- to three-fold increased risk of PCa incidence and with a two- to eight-fold increased risk of PCa mortality [45]. Because PSA determinations when properly utilized may contribute to the diagnosis and follow-up of prostate cancer [46], the effect of tomato treatment on total PSA serum levels could interfere with the clinical management. However, determination of percentage of free PSA and of free/total PSA ratio appears to be a helpful method for enhancing the specificity of total PSA evaluation [47-48] and Lycoprozen® does not change free PSA and free/total PSA values.

The overall tomato consumption may bear harmful effects on human health such as gastroesophageal reflux disease, irritable bowel syndrome, kidney stones and some urinary problems [49]. In this context, it
is worthy to be noted that, due to the preparation procedures, Lycoprozen® does not contain organic acids (citric and malic acids), significant potassium/oxalate concentration and tomato skin/seeds, responsible for these side effects.

On the basis of recent human experimentation [50] this novel dietary supplement, Lycoprozen, which is fitosterols-free may help to maintain prostate health and can contribute to the beneficial effect of adhering to the WCRF/AICR recommendations [51], by itself, when complemented with current treatments [52] and by adopting healthy lifestyles. Furthermore, because of its high deliverable antioxidant activity, Lycoprozen® consumption can be advantageous in contrasting the unhealthy effects of the excess production of free radicals induced by a variety of risk factors, including the metabolic syndrome often associated with BPH [24, 53].

Although tomatoes provide most of the dietary antioxidants in the Mediterranean-style diet, its culinary use is often associated with consumption of carbohydrates rich meals (e.g. pasta, pizza), and high calories uptake (olive oil), thus representing a risk factor for individuals with excessive body mass, obesity and metabolic syndrome. In this regard, Lycoprozen® is an exemplary source of a complex of antioxidants. With no extra calories uptake, this food supplement may represent an ideal chassis for the development of an array of more targeted food supplements to delay the onset and/or to attenuate the course of age-related chronic degenerative diseases [54].

**Conclusion**

Lycoprozen® may represent a valid option for the treatment of symptomatic BPH patients. Unlike other pharmacological treatments, Lycoprozen® is without side effects and highly accepted among patients.

**Abbreviations**

BPH: Benign prostate hyperplasia; LUTS: Lower urinary tract symptoms; PSA: prostate specific antigen; IPSS: International prostatic symptoms score

**Declarations**

**Ethics approval and consent to participate**

The study protocol was approved by the University of Foggia Ethics Committee (Nov. 8th, 2017. registration number 871-16) was carried out in agreement with the provisions of the Declaration of Helsinki. Written informed consent was obtained from all patients.

**Consent for publication**

Not applicable.
Availability of data and materials

Not applicable.

Competing interests

** These Authors (VF, SI, PGN, MP), listed in alphabetical order, are shareholders at Janus Pharma srl.

Funding

The study was supported by Janus Pharma srl. Rome, Italy

Authors’ contributions

LC, VF, SI, PGN and MP equally contributed to the conception and design of the study and to the draft of the manuscript. PGN and PM were responsible for the writing the manuscript. LC, BC, GS and GC were responsible for clinical data and management of patients. VF and PV were responsible for the production and the analytical characterization of the tomato-based food supplement. MI contributed to the manuscript. MI and AL performed the multiplex analysis of cytokines and growth factors. All authors agreed to be accountable for all aspects of the work. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

Author details

1 Urology and Renal Transplantation Unit, Department of Medical and Surgical Sciences, University of Foggia, Italy. 2 “Bonomo” Teaching Hospital, Andria (BAT), Italy. 3 Department of Medicine and Aging Sciences, Center for Advanced Studies and Technology (CAST), G. 4 d’Annunzio University, Chieti, Italy. 4 Department of Agricultural Sciences, University of Naples, Portici, Italy. 5 Wageningen University, Department of Agrotechnology & Food Science, The Netherlands. 6 Janus Pharma S.r.l., Via Giacomo Peroni 386, 00131 Roma, Italy.

Registration number

N. 871 /16
References

1. McVary KT. BPH: epidemiology and comorbidities. Am J Manag Care. 2006;12:122–S8.
2. Roehrborn CG. BPH progression: concept and key learning from MTOPS, ALTESS, COMBAT, and ALF-ONE. BJU Int. 2008;101(Suppl3):17–21.
3. McConnell JD, Roehrborn CG, Bautista OM, Andriole GL Jr, Dixon CM, Kusek JW, et al. The Long-Term Effect of Doxazosin, Finasteride, and Combination Therapy on the Clinical Progression of Benign Prostatic Hyperplasia. New England J Med. 2003;349(25):2387–98.
4. Chuhtai B, Lee R, Te A, Kaplan S. Role of Inflammation in. Benign Prostatic HyperplasiaRevUrol. 2011;13(3):147–50.
5. Ficarra V, Rossanese M, Zazzara M, Giannarini G, Abbinante M, Bartoletti R, et al. The role of inflammation in lower urinary tract symptoms (LUTS) due to benign prostatic hyperplasia (BPH) and its potential impact on medical therapy. Curr Urol Rep. 2014;15(12):463–69.
6. Kahokehr A, Vather R, Nixon A, Hill AG. Non-steroidal anti-inflammatory drugs for lower urinary tract symptoms in benign prostatic hyperplasia: Systematic review and meta-analysis of randomized controlled trials. BJU Int. 2013;111(2):304–11.
7. Fowke JH, Koyama T, Fadare O, Clark PE. Does inflammation mediate the obesity and BPH relationship? An epidemiologic analysis of body composition and inflammatory markers in blood, urine, and prostate tissue, and the relationship with prostate enlargement and lower urinary tract. PLoS One. 2016;11(6):e0156918.
8. Mohri S, Takahashi H, Sakai M, Takahashi S, Waki N, Alzawa K, et al. Wide-range screening of anti-inflammatory compounds in tomato using LC-MS and elucidating the mechanism of their functions. PLoS One. 2018;12(13):e0191203.
9. Chaudhary P, Sharma A, Singh B, Nagpal AK. Bioactivities of phytochemical present in tomato. J Food Sci Technol. 2018;55(8):2833–49.
10. Ghavipour M, Saedisomeolia A, Dialali M, Sotoudeh G, Eshraghyan MR, Moghadam AM, et al. Tomato juice consumption reduces systemic inflammation in overweight and obese females. Br J Nutr. 2013;109(11):2031–35.
11. Li YF, Chang YY, Huang HC, Wu YC, Yang MD, Chao P-M. Tomato juice supplementation in young women reduces inflammatory adipokine levels independently of body fat reduction. Nutrition. 2016;31(5):691–6.
12. Vitaglione P, Fogliano V, Stingo S, Scalfi L, Caporaso N, Morisco F. Development of a tomato-based food for special medical purposes as therapy adjuvant for patients with HCV infection. Eur J ClinNutr. 2007;61(7):906–15.
13. Pannellini T, Iezzi M, Liberatore M, Sabatini F, Iacobelli S, Rossi C, et al. A dietary tomato supplement prevents prostate cancer in TRAMP mice. Cancer Prev Res. 2010;3(10):1284–91.
14. Conlon LE, Wallig MA, Erdman JW Jr. Low-lycopene containing tomato powder diet does not protect against prostate cancer in TRAMP mice. Nutr Res. 2015;35(10);882–90.
15. Boileau TW, Liao Z, Kim S, Lemeshow S, Erdman JW Jr, Clinton SK. Prostate carcinogenesis in N-methyl-N-nitrosourea (NMU)-testosterone-treated rats fed tomato powder, lycopene, or energy-restricted diets. J Nat Cancer Inst. 2003;95(21):1578–86.

16. Canene-Adams K, Lindshield BL, Wang S, Jeffery EH, Clinton SK, Erdman JW Jr. Combinations of tomato and broccoli enhance antitumor activity in Dunning R3327-H prostate adenocarcinomas. Cancer Res. 2007;67(2):836–43.

17. Applegate C, Rowles J 3rd, Miller R, Wallig M, Clinton S, O’Brien W, et al. Dietary Tomato, but Not Lycopene Supplementation, Impacts Molecular Outcomes of Castration-resistant Prostate Cancer in the TRAMP Model. Curr Dev Nutr. 2019;3(Suppl1):eCollection. https://doi.org/10.1093/cdn/nzz030.P05-015-19.

18. Mossine VV, Chopra P, Mawhinney TP. Interaction of tomato lycopene and ketosamine against rat prostate tumorigenesis. Cancer Res. 2008;68(11):4384–91.

19. Fogliano V, Iacobelli S, Piantelli M. “Tomato powder-based composition”. 2016; US Patent App. 15/024,165.

20. Cellini A, Natali PG, Iezzi M, Piantelli M, Fogliano V, Iacobelli S. Efficacy and safety of Lycoprozen®, a novel tomato-based food supplement in patients with benign prostatic hyperplasia. Int J Nutr. 2018;3(2):1–5.

21. Irani J, Levillain P, Goujon JM, Bon D, Dore B, Aubert J. Inflammation in benign prostatic hyperplasia: correlation with prostate specific antigen value. J Urol. 1997;157(4):1301–3.

22. Badia X, Garcia-Losa M, Dal-Re R. Ten-language translation and harmonization of the International Prostate Symptom Score: developing methodology for multinational clinical trials. Eur Urol. 1997;31(2):129–40.

23. Luvizotto Rde A, Nascimento AF, Imaizumi E, Pierine DT, Conde SJ, Correa CR, et al. Lycopene supplementation modulates plasma concentrations and epididymal adipose tissue mRNA of leptin, resistin and IL-6 in diet-induced obese rats. Brit J Nutr. 2013;110(10):1803–9.

24. Kim YI, Mohri S, Hirai S, Lin S, Goto T, Ohvane C, et al. Tomato extract suppresses the production of proinflammatory mediators induced by interaction between adipocytes and macrophages. Biosci Biotechnol Biochem. 2015;79(1):82–7.

25. Cheng HM, Koutsidis G, Lodge JK, Ashor A, Siervo M, Lara J. Tomato and lycopene supplementation and cardiovascular risk factors: A systematic review and meta-analysis. Atherosclerosis. 2017;257:100–8.

26. Gravas S, Cornu JN, Drake MJ. EAU Guidelines on Management of non-neurogenic male lower urinary tract symptoms. 5.2 Pharmacological treatment. 2018;17–25, ISBN 978-94-92671-01-1. http://uroweb.org/guidelines/compilations-of-all-guidelines/.

27. Wertz K, Siler U, Goralczyk R. Lycopene: modes of action to promote prostate health. Arch Biochemical Biophys. 2004;430(1):127–34.

28. Kouka P, Chatzieffraigimidi GA, Raftis G, Stagos D, Angelis A, Stathopoulos P, et al. Antioxidant effects of an olive oil total polyphenolic fraction from a Greek Olea europaea variety in different cell cultures.
29. Zhao Q, Yang F, Meng L, Chen D, Wang M, Lu X, et al. Lycopene attenuates chronic prostatitis/chronic pelvic pain syndrome by inhibiting oxidative stress and inflammation via the interaction of NF-κB, MAPKs, and Nrf2 signaling pathways in rats. Andrology. 2020;8(3):747–55.

30. Fernández-Bedmar Z, Anter J, Alonso Moraga Á. Anti/genotoxic, longevity inductive, cytotoxic, and clastogenic-related bioactivities of tomato and lycopene. Environ Mol Mutagen. 2018;59(5):427–37.

31. Roehrborn CG, McConnell J. Etiology, pathophysiology, epidemiology and natural history of benign prostatic hyperplasia. In Walsh P, Retik A, Vaughan E, Wein A, editors. Campbell’s Urology 8th Edition. Philadelphia: Saunders; 2002. P.1297–1333.

32. Umtergasser G, Madersbacher S, Berger P. Benign prostatic hyperplasia: age related tissue remodeling. Exp Gerontol. 2005;40(3):121–8.

33. Kim HS, Bowen P, Chen L, Duncan C, Ghosh, Sharifi R, et al. Effects of tomato sauce consumption on apoptotic cell death in prostate benign hyperplasia and carcinoma. Nutr Cancer. 2003;47(1):40–7.

34. Liu C, Lian F, Smith DE, Russel RM, Wang X-D. Lycopene supplementation inhibits lung squamous metaplasia and induces apoptosis via up-regulating insulin-like growth factor-binding protein 3 in cigarette smoke-exposed ferrets. Cancer Res. 2003;63(12):3138–44.

35. Applegate CC, Rowles JL, Erdman JW. Can Lycopene Impact the Androgen Axis in Prostate Cancer?: A Systematic Review of Cell Culture and Animal Studies. Nutrients 2019;11(3) doi:10.3390/nu11030633.

36. Schatteman PH, Hoekx L, Wyndaele JJ, Jeuris W, Van Marck E. Inflammation in prostate biopsies of men without prostate malignancy or clinical prostatitis: correlation with total serum PSA and PSA density. Eur Urol. 2000;37(4):404–12.

37. Meert T, Baten E, van Renterghem K. Clinical importance of histopathological inflammation in patients with lower urinary tract symptoms due to benign prostatic hyperplasia: A prospective study of 222 patients. Curr Urol. 2017;10(3):150–3.

38. Chen L, Stacewicz-Sapuntzakis M, Duncan C, Sharifi R, Ghosh L, van Breemen R, et al. Oxidative DNA damage in prostate cancer patients consuming tomato sauce-based entrees as a whole-food intervention. J Natl Cancer Inst. 2001;93(24):1872–79.

39. Jatoi A, Burch P, Hillman D, Vanyo JM, Dakhil S, Nikcevich D, et al. A tomato- based, lycopene-containing intervention for androgen-independent prostate cancer: results of a Phase II study from the North Central Cancer Treatment Group. Urology. 2007;69(2):289–94.

40. Bunker CH, McDonald AC, Evans RW, de la Rosa N, Boumosleh JM, Patrick A. A randomized trial of lycopene supplementation in Tobago men with high prostate cancer risk. Nutr Cancer. 2007;57(2):130–7.

41. Paur I, Lilleby W, Kjølsrud Bohn S, Hulande E, Klein W, Vlatkovic L, et al. Tomato-based randomized controlled trial in prostate cancer patients: Effect on PSA. Clin Nutr. 2017;36(3):672–9.

42. 10.3389/fphar
43. Yahfoufi N, Alsadi N, Jambi M, Matar C. The immunomodulatory and anti-inflammatory role of polyphenols. Nutrients. 2018;10(11):1618. Doi 10.3390/nu10111618.
44. Yuan JJ, Coplen DE, Petros JA, Figenshau RS, Ratliff TL, Smith DS, et al. Effects of rectal examination, prostatic massage, ultrasonography and needle biopsy on serum prostate specific antigen levels. J Urol. 1992;147(3Pt2):810–4.
45. Ørsted DD, Bojesen SE, Nielsen SF, Nordestgaard BG. Association of Clinical Benign Prostate Hyperplasia with Prostate Cancer Incidence and Mortality Revisited: A Nationwide Cohort Study of 3 009 258 men. Eur Urol. 2011;60(4):691–8.
46. Huang JG, Campbell N, Goldenberg SL. PSA and beyond: Biomarkers in prostate cancer. Sc Med J. 2014;56(7):334–41.
47. Morote J, Ravento CX, Lorente JA, Miguel A. Lopez-Pacios MA, Encabo G, et al. Measurement of free PSA in the diagnosis and staging of prostate cancer. Int J Cancer. 1997;71(5):756–9.
48. Walz J, Haese A, Scattoni V, Steuber T, Chun FKH, Briganti A, et al. Percent free prostate-specific antigen (PSA) is an accurate predictor of prostate cancer risk in men with serum PSA 2.5 ng/ml and lower. Cancer. 2008;113(10):,2695–703.
49. Salehi B, Sharifi-Rad R, Sharopov F, Namiesnik J, Rooitnan A, Kamle M, et al. Beneficial effects and potential risks of tomato consumption for human health: An overview. Nutrition. 2019;62:201–8.
50. Chen P, Zhang W, Wang X, Zhao K, Singh Negi D, Zhuo L, et al. Lycopene and Risk of Prostate Cancer: A Systematic Review and Meta-Analysis. Medicine. 2015;94(33):e 1260.
51. Er V, Lane JA, Martin RM, Emmet P, Gilbert R, Avery KN, et al. Adherence to Dietary and Lifestyle Recommendations and Prostate Cancer Risk in the Prostate Testing for Cancer and Treatment (ProtecT) Trial. Cancer Epidemiol Biomarkers Prev. 2014;23(10):2066–77.
52. Minutoli L, Altavilla D, Marini H, Rinaldi M, Irrera N, Pizzino G, et al. Inhibitors of apoptosis proteins in experimental benign prostatic hyperplasia: effects of serenoa repens, selenium and lycopene. J Biomed Sci. 2014;21(1). doi:10.1186/1423-0127-21-19.
53. Han GM, Meza JL, Soliman GA, Islam KM, Aatanabe-Galloway S. Higher levels of serum lycopene are associated with reduced mortality in individuals with metabolic syndrome. Nutr Res. 2016;36(5):402–7.
54. Li Y, Wang H, Zhang Y, Martin C. Can the world’s favorite fruit, tomato, provide a biosynthetic chassis for high-value metabolites? Plant Cell Rep. 2018;37(10):1443–50.

Figures
Figure 1

Total PSA levels pre and post Lycoprozen® treatment. All patients (left panel) and patients with PSA > 10 ng/ml (right panel)