DOI: *10.4081/aiua.2025.13412*

ORIGINAL PAPER

Discovering a new nutraceutical based on pollen extract and teupolioside: A prospective monocentric study evaluating its role in alleviating lower urinary tract symptoms in benign prostatic hyperplasia patients

Mattia Lo Re [1, 2*], Marta Pezzoli [1, 2*], Anna Cadenar [1, 2], Elettra Fuligni [1, 2], Leonardo Gajo [1, 2], Andrea Minervini [1], Andrea Cocci [1, 2]

[1] Unit of Oncologic Minimally Invasive Urology and Andrology, University of Florence, Careggi Hospital, Florence, Italy;
[2] Department of Experimental and Clinical Medicine, University of Florence, Florence, Italy.

[*] *These authors contributed equally to this work.*

Summary *Background: Benign prostatic hyperplasia (BPH) is a common condition in men over 50, leading to lower urinary tract symptoms (LUTS). A nutraceutical containing pollen extract (Graminex® G96®) and teupolioside has shown potential in alleviating LUTS by targeting inflammation and dihydrotestosterone production. This prospective, monocentric study enrolled 60 patients with mild to moderate LUTS due to BPH.*

Methods: Participants received one tablet daily for three months. Assessments included the International Prostate Symptom Score (IPSS), quality of life (QoL), uroflowmetry, post-void residual (PVR), and sexual function (IIEF-5, MSHQ EjD).

Results: Fifty-three patients completed follow-up. Significant improvements were observed in IPSS and QoL ($p < 0.001$), with scores decreasing from 14 (11-16) at baseline to 10 (8-12) at three months and decreasing from 3 (2-3) to 2 (2-2), respectively. Uroflowmetry parameters (Q_{max} and PVR) improved, increasing from 12 (11-16) ml/s to15 (11-17) ml/s and decreasing from 50 (30-55) ml to 35 (25-45) ml, respectively, without statistical significance ($p > 0.05$). Sexual function and PSA levels remained stable, with no significant adverse effects reported.

Conclusion: The combination of pollen extract and teupolioside effectively alleviates LUTS in BPH patients with a favorable safety profile, particularly in avoiding sexual dysfunction.

KEY WORDS: Benign prostatic hyperplasia; Nutraceutical; Lower urinary tract symptoms.

Submitted 21 Nvember 2024; Accepted 12 December 2024

INTRODUCTION

Benign prostatic hyperplasia (BPH) is a prevalent condition among men over 50 years old, often leading to *lower urinary tract symptoms* (LUTS) (1). Chronic inflammation is pivotal in the pathogenesis and progression of BPH, where immune cells in the prostate release pro-inflammatory cytokines and free radicals, exacerbating the inflammatory process (2).

α1-blockers and 5α-reductase inhibitors are established therapies, yet their impact on erectile and ejaculatory function can be bothersome (3, 4). Consequently, there is a growing interest in nutraceutical agents for managing BPH. Within this context, Xipag® (*IDI Integratori Dietetici Italiani S.r.l., Aci Bonaccorsi, CT, Italy*), formulated with pollen extract (Graminex® G96®; 500 mg) and teupolioside (Teupol 25P; 60 mg), has emerged as a promising BPH treatment, supported by research into its key components (5).

Graminex®, derived from Secale cereale, has demonstrated anti-inflammatory, anti-edema, and antioxidant effects in ex vivo studies on rat prostate specimens, owing to its complex composition rich in amino acids, enzymes, minerals, and bioactive compounds (6). Pollen extracts have been researched for their efficacy in managing prostatitis and pelvic pain, with animal models showing effectiveness in reducing stromal proliferation and glandular inflammation (7, 8). Furthermore, clinical trials have highlighted significant improvements in chronic pelvic pain and LUTS with pollen extract, often surpassing the efficacy of tadalafil (9).

Teupolioside, derived from Ajuga reptans cell cultures, has shown promise in preliminary *in vitro* studies by reducing *dihydrotestosterone* (DHT) production through NADPH oxidation and exhibiting notable anti-inflammatory properties (5).

This combined approach offers a novel therapeutic strategy for alleviating LUTS in BPH patients, targeting both inflammation and DHT production. This study aims to assess the efficacy of Xipag® in managing LUTS among BPH patients.

MATERIALS AND METHODS

Study design and protocol

This single-center observational study was conducted from March to September 2024.

This study was awarded at the 97th SIU Congress in Bari on October 11th-13th, 2024.

Patients presenting mild or moderate LUTS related to BPH were enrolled after signing a written informed consent.

All enrolled patients completed three baseline (T0) questionnaires: the *International Prostatic Symptoms Score-Quality of Life* (IPSS-QoL), the *Male Sexual Health Questionnaire Ejaculatory Dysfunction* (MSHQ EjD - Short Form), and the *International Index of Erectile Function-5* (IIEF-5). Additionally, patients underwent a blood examination to evaluate *prostate-specific antigen* (PSA) levels and performed uroflowmetry with *post-void residual* (PVR) evaluation.

Patients who consented to participate in the study received one tablet per day of Xipag® for three months. Clinical evaluations, using the same four baseline questionnaires, PSA dosage, and uroflowmetry with PVR assessment, were conducted at one month (T1) and three months (T2) after the start of the treatment. At T2, patients were also asked about their willingness to continue the use of Xipag®.

The study was conducted in line with Good Clinical Practice guidelines and with the ethical principles of the Declaration of Helsinki. Before the beginning of the study, all participants signed the written informed consent. No placebo run-in period was performed.

Inclusion and exclusion criteria

Inclusion criteria were age over 40 years, diagnosis of LUTS related to BPH, mild to moderate LUTS (IPSS score 8-19), sexually active patients (IIEF-5 score ≥ 17) and any prostate volume. Exclusion criteria included clinical suspicion of prostatic cancer (based on rectal examination or suspicious elevation of PSA levels) or bladder cancer, neurological bladder, urethral stricture, bacterial prostatitis or recurrent urinary tract infections, previous pelvic radiation therapy, use of alpha-blockers, 5-alpha-reductase inhibitors, or *phosphodiesterase-5 inhibitors* (PDE5i), and allergies to components of Xipag®.

Outcomes

The primary objective was to evaluate the efficacy of Xipag® in improving urinary symptoms and function, as measured by IPSS, *maximum urinary flow rate* (Q_{max}), and PVR.

The secondary objective was to assess changes in sexual function, using IIEF-5 and MSHQ-EjD scores, and analyze any changes in PSA levels.

Statistical analysis

Values for quantitative variables are expressed as median and *interquartile range* (IQR).

Comparisons between pairs of values (baseline - each time point) were performed using a Wilcoxon signed rank test, with a p-value < 0.05 deemed to be statistically significant. All statistical analyses were conducted using SPSS 21.0 (*IBM Corporation, Armonk, NY, USA*).

Results

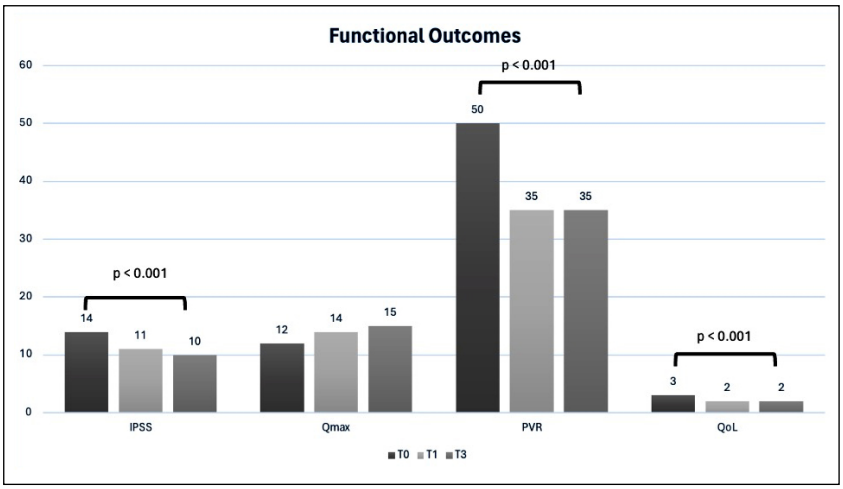
A total of 60 patients were consecutively enrolled in this study. Of these, 6 were lost to follow-up and 1 was excluded due to starting alpha-blocking therapy on his family doctor's advice. Consequently, 53 patients completed both the 1 and 3-month follow-ups. The age of participants was 55 (45-64) years, with a *body mass index* (BMI) of 24.5 (23.2-26.3). Significant improvements in urinary symptoms were observed at both time points ($p < 0.001$) (Table 1). IPSS score decreased from 14 (11-16) at baseline to 11 (9-13) at 1 month and 10 (8-12) at 3 months. IPSS *Quality of Life* (QoL) parameter also improved, decreasing from 3 (2-3) at T0 to 2 (2-2) at T1 and 2 (2-2) at T2. Uroflowmetry parameters improved, even without a statistical significance ($p < 0.05$): Qmax increased from 12 (11-16) ml/s at T0 to 14 (11-16) ml/s at T1 and 15 (11-17) ml/s at T2 meanwhile PVR decreased from 50 (30-55) ml at T0 to 35 (25-40) ml at T1 and 35 (25-45) ml at T2 (Figure 1).

Table 1.
Functional outcomes at different timepoints.

	Baseline, n = 60	1 month, n = 53	3 months, n = 53	P
IPSS, median (IQR)	14 (11-16)	11 (9-13)	10 (8-12)	0.001
IPSS QoL, median (IQR)	3 (2-3)	2 (2-2)	2 (2-2)	0.001
Q_{max} (ml/s), median (IQR)	12 (11-16)	14 (11-16)	15 (11-17)	> 0.05
PVR (ml), median (IQR)	50 (30-55)	35 (25-40)	35 (25-45)	0.001
PSA (ng/ml), median (IQR)	1.54 (1.34-2.35)	1.35 (1.22-2.12)	1.34 (1.12-2.30)	> 0.05

IQR: interquartile range; Q_{max}: maximum flow rate; PVR: post-void residual; IPSS: International Prostatic Symptoms Score; QoL: Quality of Life; MSHQ: men sexual health questionnaire.

Figure 1.
Graphical representation of functional outcomes over different time points.



Q_{max}: maximum flow rate; PVR: post-void residual; IPSS: International Prostatic Symptoms Score; QoL: Quality of Life.

Regarding sexual function, there was a slight increase in both IIEF5 and MSHQ EjD scores, though these changes were not statistically significant ($p > 0.05$). PSA levels remained stable at T1 and showed a slight decrease at T2, but no statistically significant changes were detected ($p > 0.05$).
After 3 months of treatment, 44 patients (83.2%) expressed their willingness to continue. Three patients (5.7%) reported no significant improvement in LUTS and expressed the desire to switch to another therapy. Six patients (11.3%) with initially mild LUTS experienced intolerance to daily therapy, leading them to want to discontinue the treatment, with the possibility of reevaluation if symptoms worsened.
Overall, no ADRs were recorded. After three weeks of using Xipag®, one patient developed a mild skin rash, which was resolved spontaneously. The patient continued the treatment, and no similar events occurred, suggesting that the rash was not likely an ADR related to the nutraceutical.

Discussion

In this study, we evaluated the efficacy and safety of a novel nutraceutical, Xipag®, which contains Teupolioside (Teupol 60 mg) and Pollen Extract (Graminex® G96® 500 mg), for the treatment of LUTS associated with BPH. As previously documented in the literature, the effectiveness of Teupolioside in addressing prostatic hypertrophy and that of Pollen Extract in alleviating symptoms such as chronic pelvic pain and irritation are well established (10), making this product particularly promising for managing moderate LUTS.
Our findings offer several insights into the potential utility of this product.
First, only three patients (5.7%) reported no significant improvement in LUTS and expressed a desire to switch to alternative therapies. Conversely, all other participants experienced a significant improvement in symptoms as measured by the *International Prostate Symptom Score* (IPSS), alongside a non-significant improvement in urinary flow rate (Q_{max}). Our study corroborates the findings of *Muraca et al.*, who first demonstrated the potential benefits of Xipag® in a pilot study (11), noting an IPSS improvement from a mean baseline score of 13.3 ± 6.1 to a 3-month decrease of 22.7-88.9% (mean 55.2 ± 23.6%). This consistency with prior research bolsters the credibility of our results and suggests that Xipag® may represent an effective therapeutic option for patients with BPH.
Secondly, while nutraceuticals have garnered attention in the management of BPH, their efficacy remains a subject of debate. A recent systematic review by *Franco et al.* (12) did not find significant evidence supporting the efficacy of nutraceuticals in various trials. However, another systematic review by *Novara et al.* (13) reported significant efficacy on outcomes such as IPSS, IPSS QoL, and Q_{max} in patients treated with Permixon, which also exhibited a favorable safety profile. In this context, our study demonstrates that a phytotherapeutic agent like Xipag® can achieve symptom improvements in selected patients, comparable to those observed in studies of nutraceuticals like Serenoa repens.
Thirdly, although the symptom relief observed with Xipag® was less pronounced than that reported in studies of alpha-blockers, our study is noteworthy for the absence of adverse effects on sexual function, as we do not detect a significant change in the IIEF and MSHQ ED questionnaire.
This is a considerable advantage, as conventional alpha-blocker treatments are often associated with side effects, such as ejaculatory dysfunction, which can lead to therapy discontinuation (14, 15). The tolerability of Xipag® thus positions it as an attractive option for patients seeking symptom relief – particularly those with mild symptoms – without the risk of side effects.
Nonetheless, our study is not devoid of limitations. One notable limitation is the relatively short follow-up period of three months. While significant improvements were observed within this timeframe, longer follow-up is necessary to assess the sustainability of Xipag®'s effects. Additionally, the observational nature of our study introduces potential biases, as it lacks the rigor of a *randomized controlled trial* (RCT). Future research should aim to utilize RCT methodologies to further validate the efficacy of Xipag® and compare its performance against placebo and established BPH treatments in a controlled environment.

Conclusions

In conclusion, this study represents the largest cohort to date evaluating the effects of Xipag® on BPH-related symptoms, with 53 patients completing the study. The size of our cohort enables a more robust analysis and provides valuable data to the limited existing literature on Xipag® and contributes to the growing body of evidence supporting the use of nutraceuticals in managing BPH-related symptoms, particularly in cases where conventional therapies may lead to undesirable side effects.

Declarations

Ethical approval: *The procedures used in this study adhere to the tenets of the Declaration of Helsinki.*
The patients/participants provided their written informed consent to participate in this study.

Availability of data and material: *All inquiries can be directed to the corresponding author.*

Competing interests: *The authors certify that there is no conflict of interest with any financial organization regarding the material discussed in the manuscript.*

Funding: *The authors report no involvement in the research by the sponsor that could have influenced the outcome of this work.*

Authors' contributions: *MLR and MP have given substantial contributions to the conception and the design of the manuscript. AC, LG AND EF to the acquisition of the data; MLR to the analysis and interpretation of the data. MLR, and MP have participated to drafting the manuscript, AM and AC revised it critically. All authors read and approved the final version of the manuscript.*

Acknowledgments: *Not applicable.*

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Correspondence

Mattia Lo Re, MD
mattialore1994@gmail.com

Marta Pezzoli, MD (Corresponding Author)
marta.pezzoli@unifi.it
University of Florence, Careggi Hospital, 50100 Florence, Italy

Anna Cadenar, MD
anna.cadenar@unifi.it

Elettra Fuligni, MD
elettra.fuligni@unifi.it

Leonardo Gajo, MD
leonardo.gajo@unifi.it

Andrea Minervini, MD
andrea.minervini@unifi.it

Andrea Cocci, MD
cocci.andrea@gmail.com