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ORIGINAL PAPER

Sexual safety and efficacy of a pollen extract and teupolioside-based supplement in men with benign prostatic hyperplasia: A prospective observational study

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Summary

Background: *Benign prostatic hyperplasia (BPH) is a common age-related condition that often results in lower urinary tract symptoms (LUTS), reduced quality of life, and sexual dysfunction. Conventional pharmacotherapies, while effective, are frequently associated with adverse effects on sexual and ejaculatory function. This study evaluated the sexual safety and clinical efficacy of a dietary supplement containing pollen extract and teupolioside, in men with BPH.*

Methods: *In this prospective, single-arm observational study, 25 men with moderate LUTS due to BPH received daily pollen extract and teupolioside supplementation for 90 days. The primary endpoints were sexual function (International Index of Erectile Function, IIEF-5), ejaculatory function (Male Sexual Health Questionnaire–Ejaculatory Dysfunction, MSHQ-EjD), quality of life (IPSS-QoL), and patient global impression of improvement (PGI-I). Secondary endpoints included changes in urinary flow (Q_{max}) and LUTS severity (International Prostate Symptom Score, IPSS). Assessments were conducted at baseline, 1 month, and 3 months.*

Results: *Sexual and ejaculatory functions remained stable over the treatment period, with no statistically significant deterioration observed. QoL improved significantly by the 3-month mark (IPSS-QoL median score reduced from 3 to 2; $p < 0.008$), and PGI-I scores reflected high patient satisfaction (median 2, IQR 1). Q_{max} significantly increased from 12.4 mL/s at baseline to 15.5 mL/s at 3 months ($p < 0.001$), and IPSS scores significantly declined from 11 to 8 ($p < 0.008$), indicating improved urinary function.*

Conclusions: *The pollen extract and teupolioside supplementation was well tolerated and associated with improved QoL and urinary outcomes, without compromising sexual or ejaculatory function. These findings support its potential as a non-pharmacologic adjunct in the management of BPH, particularly in patients concerned about sexual side effects. Further randomized controlled studies are warranted to confirm these results.*

KEY WORDS: *Benign prostatic hyperplasia; Teupolioside; Nutraceutical; Sexual safety; Lower urinary tract symptoms.*

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INTRODUCTION

Benign prostatic hyperplasia (BPH) is a prevalent, nonmalignant condition characterized by the proliferation of prostatic stromal and epithelial cells, typically occurring in aging males. This hyperplastic growth may contribute to lower urinary tract obstruction and the development of *lower urinary tract symptoms* (LUTS), which negatively affect patients' quality of life and functional status (1). In addition, chronic prostatic inflammation has been implicated in the progression of BPH and is associated with increased prostate volume and symptom severity (2, 3).

Pharmacologic management of BPH primarily includes α1-adrenergic receptor antagonists and 5α-reductase inhibitors. However, these agents frequently cause adverse effects such as orthostatic hypotension, reduced libido, and ejaculatory dysfunction, which can impair adherence and limit long-term utility (1, 4). Accordingly, there is increasing clinical interest in nutraceuticals and plant-derived therapies that may offer symptomatic relief with a more favorable side-effect profile.

Xipag® is a dietary supplement composed of pollen extract and teupolioside - a polyphenolic glycoside extracted from Ajuga reptans that exhibits 5α-reductase inhibitory activity, potentially modulating androgenic signaling in prostatic tissue (5). Pollen extract, rich in phytosterols and anti-inflammatory compounds, may enhance therapeutic outcomes through its antioxidative, anti-inflammatory, and muscle-relaxant properties (6).

This study aimed to evaluate the clinical efficacy of *Xipag*® in men with BPH, with primary endpoints focused on sexual function, ejaculatory function, *quality of life* (QoL), and *patient global impression of improvement* (PGI-I). Secondary endpoints included urodynamic parameters and LUTS symptom reduction.

METHODS

This prospective, single-arm observational study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the institu-

tional Ethics Committee (*STS CE Lazio1/N-945, "Lazio 1", San Camillo Forlanini Hospital, Rome, Italy*). Written informed consent was obtained from all participants.

A total of 25 male patients with BPH-associated LUTS were enrolled. Inclusion criteria comprised age ≥ 18 years, serum prostate-specific antigen (PSA) ≤ 4 ng/mL, prostate volume ≤ 60 mL, Q_{max} ≤ 15 mL/s, and *post-void residual* (PVR) volume < 150 mL. Patients were excluded if they had urinary tract infection, urological malignancy, prior prostate surgery, significant comorbidities (e.g., neurogenic bladder, uncontrolled diabetes), or hypersensitivity to the supplement's components.

Eligible participants received a daily regimen of *Xipag®* (*IDI Integratori Dietetici Italiani S.r.l., Aci Bonaccorsi, CT, Italy*), administered as one tablet per day over a 90-day period. Each daily dose of *Xipag®* , contained the following active compounds: pollen extract (*Graminex® G96®; 500 mg*) and teupolioside (*Teupol 25P; 60 mg*). No additional pharmacological treatments targeting BPH were prescribed during the study period to avoid confounding effects.

At baseline (T0), patients signed informed consent, underwent clinical evaluation, uroflowmetry, ultrasonographic evaluation of PVR.

Patient-reported outcomes measures (PROMs) were evaluated using validated symptom and QoL questionnaires.

Evaluations were conducted at baseline (T0), 1 month (T1), and 3 months (T2, end of treatment). Primary outcomes were assessed using: *International Index of Erectile Function* (IIEF-5), *Male Sexual Health Questionnaire-Ejaculatory Dysfunction* (MSHQ-EjD), *IPSS-QoL domain, Patient Global Impression of Improvement* (PGI-I). Secondary outcomes included uroflowmetry (Q_{max}) and the *International Prostate Symptom Score* (IPSS).

In this study, *artificial intelligence* (AI), specifically ChatGPT (*chatgpt.com*), was used solely for reviewing the English language in its grammar, syntax, and style, without affecting content, citations, or interpretative and conclusive discussions.

Statistical analysis

Continuous variables were summarized using medians and *interquartile ranges* (IQRs). The Wilcoxon signed-rank test was used to compare scores at T0, T1, and T2. A p-value < 0.05 was considered statistically significant.

Results

A total of 25 patients completed the study protocol. Baseline characteristics of study population were the following: median age 55 years (interquartile range, IQR 14); median prostate volume 44 ml (IQR 15); median PSA 1.4 ng/ml (IQR 1.5). PROMs and functional results during follow-up are summarized in Table 1.

Among the primary endpoints, sexual function, as measured by the *International Index of Erectile Function* (IIEF-5), showed no significant changes across time points. The median score was 21 (IQR: 3) at both baseline and 1 month (p = 0.5), with a slight increase to 22 (IQR: 4) at 3 months (p = 0.08).

Ejaculatory function, evaluated through the MSHQ-EjD function domain, demonstrated stable median values: 13 (IQR: 3) at baseline, 12 (IQR: 2) at 1 month (p = 0.8), and 12 (IQR: 3) at 3 months (p = 0.4), indicating no significant change. The MSHQ-EjD bother domain remained unchanged between baseline and 1 month with a median of 1 (IQR: 3; p = 0.7) and decreased slightly to 0 (IQR: 2) at 3 months, though not reaching statistical significance (p = 0.08).

Quality of life (QoL), assessed via the IPSS-QoL domain, remained stable at 1 month with a median of 3 (IQR: 1) compared to baseline (3, IQR: 2; p = 0.8), but improved significantly at the 3-month follow-up to a median of 2 (IQR: 1; p < 0.008). A critical component of patient-centered care, the *Patient Global Impression of Improvement* (PGI-I), confirmed the subjective benefit reported by patients. At the 3-month evaluation, the median PGI-I score was 2 (IQR: 1), denoting that most patients perceived their condition as "*much improved*" or "*very much improved*". Importantly, more than half of the participants (52%) expressed a desire to continue the treatment beyond the study period, indicating high patient satisfaction and acceptability of the supplement.

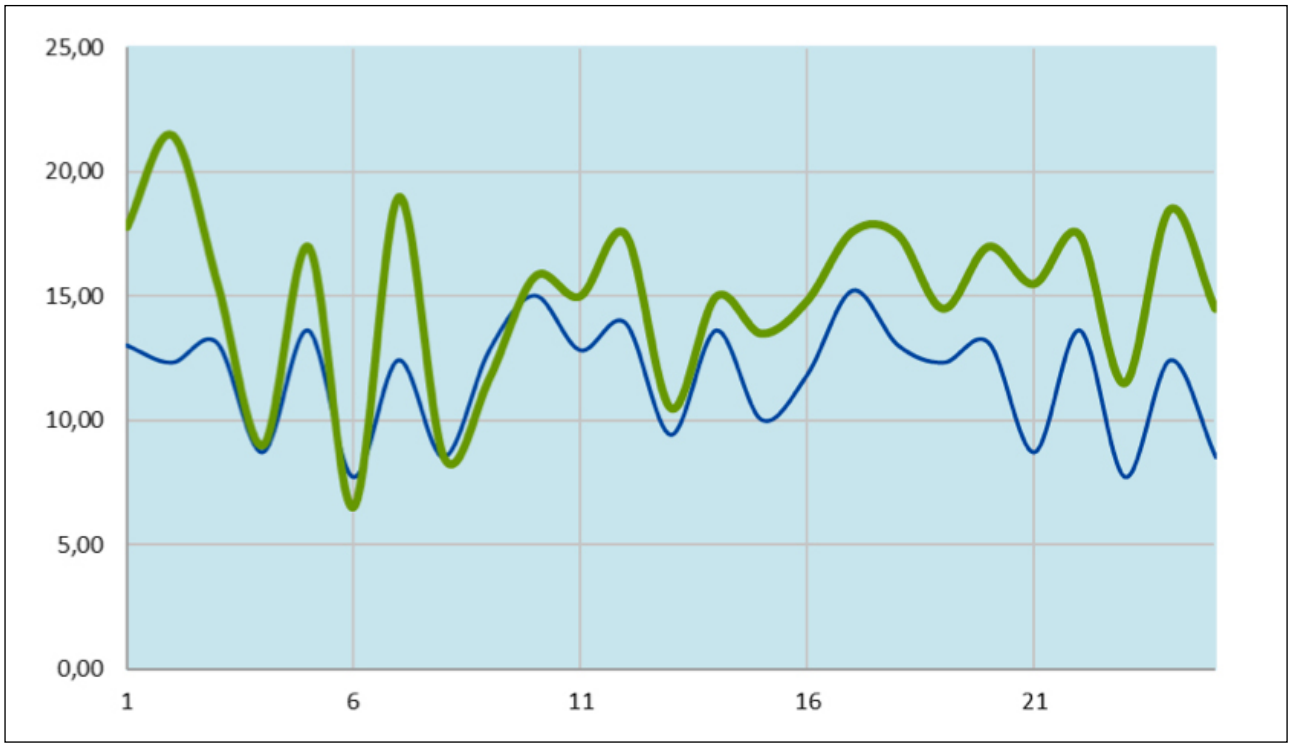
Regarding the secondary endpoints, a progressive and ultimately statistically significant enhancement in urody-

Table 1.
Baseline characteristics and results of questionnaires and functional outcomes during follow-up.

N = 25	Baseline	1-month	P-value *	3-months	P-value **
IIEF, median (IQR)	21 (3)	21 (3)	0.5	22 (4)	0.08
MSHQ-EjD ejaculatory function domain, median (IQR)	13 (3)	12 (2)	0.8	12 (3)	0.4
EJ-MSHQ bother item, median (IQR)	1 (3)	1 (3)	0.7	0 (2)	0.08
Q_{max}, median (IQR)	12.4 (4.6)	13.5 (7.6)	0.1	15.5 (4)	< 0.001
PVR (ml), median (IQR)	15 (20)	12.5 (20)	0.1	12.5 (25)	< 0.01
IPSS (LUTS domain), median (IQR)	11 (4)	10 (8)	0.4	8 (2)	< 0.008
IPSS-QoL (QoL domain), median (IQR)	3 (2)	3 (1)	0.8	2 (1)	< 0.008
PGI-I				2 (1)	

** p-value between 1-month follow-up and baseline.*
*** p-value between 3-months and baseline follow-up.*
IIEF International Index of Erectile Function (IIEF-5); IPSS: International Prostate Symptom Score; IPSS-QoL: International Prostate Symptom Score-Quality of Life;
Male Sexual Health Questionnaire–Ejaculatory Dysfunction (MSHQ-EjD); PGI-I: Patient Global Impression of Improvement; PVR: Post-void residual; PVR: Post-void residual volume.

Figure 1.
Uroflowmetry (y = Q_{max}) in the 25 patients (x = patients). The blue line represents baseline flow characteristics; the green line represents the median trend of the traces at the end of the 90-day treatment period.



namic parameters was observed. At baseline, the median maximum urinary flow rate (Q_{max}) was 12.4 ml/s (IQR: 4.6). An increase to 13.5 ml/s (IQR: 7.6) was observed at 1 month, though this change was not statistically significant (p = 0.1). At 3 months, Q_{max} significantly improved to 15.5 ml/s (IQR: 4), with a p-value < 0.001, indicating a clinically relevant improvement in urinary flow (Figure 1). The *International Prostate Symptom Score* (IPSS) for LUTS showed a median baseline value of 11 (IQR: 4), which slightly decreased to 10 (IQR: 8) at 1 month (p = 0.4). A significant reduction was noted at 3 months, with a median score of 8 (IQR: 2) (p < 0.008), reflecting symptom alleviation over time.

Discussion

The findings of this study offer preliminary yet compelling evidence supporting the clinical utility of *Xipag*® – a dietary supplement composed of pollen extract and teupolioside – in the management of BPH, particularly in patients presenting with moderate LUTS and a preserved sexual function profile.

Crucially, our analysis demonstrated that the supplement had a favorable effect on the primary outcomes of sexual function, ejaculatory function, QoL, and PGI-I. Although sexual function and ejaculatory parameters did not exhibit statistically significant changes, they remained stable throughout the study period. The IIEF-5 showed no significant variation: median values remained 21 (IQR: 3) at baseline and T1 (p = 0.5), with a non-significant increase to 22 (IQR: 4) at T2 (p = 0.08). This suggests that the supplement neither impaired nor meaningfully enhanced erectile function. Similarly, ejaculatory function assessed by the MSHQ-EjD function domain, remained unchanged, with median scores of 13 (IQR: 3) at baseline, 12 (IQR: 2) at T1 (p = 0.8), and 12 (IQR: 3) at T2 (p = 0.4). The MSHQ-EjD bother domain showed a mild, non-significant decline in bother scores from a median of 1 (IQR: 3) at baseline and T1 to 0 (IQR: 2) at T2 (p = 0.08). This is particularly relevant in the context of BPH treatment, where commonly prescribed drugs such as α1-blockers and 5α-reductase inhibitors are known to impair sexual performance and ejaculatory function. The preservation of sexual health seen with *Xipag*® is thus not merely a neutral finding, but a comparative advantage that may enhance treatment adherence and patient satisfaction. The observed non-significant upward trend in IIEF-5 scores at 3 months suggests a possible mild benefit that warrants further investigation in a larger cohort.

Perhaps the most notable result in this domain was the significant enhancement in QoL, as evidenced by the IPSS-QoL score at the 3-month mark. QoL scores remained unchanged at 1 month (median 3, IQR: 1; p = 0.8), but improved significantly at 3 months (median 2, IQR: 1; p < 0.008). This improvement paralleled a substantial proportion of patients reporting subjective symptom relief via the PGI-I, indicating a concordance between objective questionnaire data and patient experience - an essential aspect of any therapeutic intervention, particularly for chronic and quality-of-life-limiting conditions such as BPH.

In terms of secondary endpoints, the supplement produced significant improvements in both objective and subjective urological measures. The Q_{max} showed a statistically and clinically meaningful increase by the end of the

study, suggesting a reduction in urinary tract obstruction or improvement in bladder emptying. The Q_{max} demonstrated a progressive improvement over time. At baseline, the median Q_{max} was 12.4 ml/s (IQR: 4.6), increasing to 13.5 ml/s (IQR: 7.6) at T1. Although the early increase did not achieve statistical significance ($p = 0.1$), a significant enhancement was observed at T2, with Qmax reaching 15.5 ml/s (IQR: 4) ($p < 0.001$). From a baseline median score of 11 (IQR: 4), IPSS decreased to 10 (IQR: 8) at T1 ($p = 0.4$), and significantly declined to 8 (IQR: 2) at T2 ($p < 0.008$) indicating that symptom relief may accrue with continued administration - potentially reflecting the gradual anti-inflammatory and anti-androgenic effects of the supplement's active components.

The mechanism of action of *Xipag*® appears to be multifactorial. Teupolioside has demonstrated inhibitory effects on 5α-reductase, potentially decreasing intraprostatic dihydrotestosterone levels and thereby reducing prostatic volume and obstruction. This pathway is analogous to that targeted by finasteride or dutasteride, but without the hormonal side effects that frequently accompany those medications. In parallel, pollen extract offers a rich profile of phytosterols, flavonoids, and essential fatty acids, contributing antioxidative and anti-inflammatory properties, along with smooth muscle relaxation. Together, these mechanisms provide a plausible pharmacological basis for the observed improvements in urinary flow and symptom burden, as well as the absence of detrimental effects on sexual function.

These findings are broadly consistent with prior literature, including clinical studies by *Lo Re et al.* (7) and *Muraca et al.* (8), which evaluated the same fixed-dose combination. Both studies reported reductions in IPSS scores and enhancements in QoL, alongside excellent tolerability and patient adherence. Our study reinforces these conclusions while further emphasizing the sexual safety profile of the supplement - a domain that remains underrepresented in BPH supplement research.

Nevertheless, a number of limitations must be acknowledged. The sample size was relatively small (n = 25), limiting statistical power and generalizability. The lack of a control group – placebo or otherwise – precludes definitive causal inference, and the single-arm design introduces potential for performance, observer, and expectation bias. Additionally, the 3-month duration, while sufficient to demonstrate initial therapeutic effects, does not provide insight into long-term efficacy, sustainability of benefit, or potential delayed adverse events. These concerns are particularly relevant given the chronic nature of BPH, which often requires extended treatment timelines.

Despite these constraints, the absence of adverse events, in combination with significant improvements in QoL, urinary function, and patient-reported outcomes, positions *Xipag*® as a viable non-pharmacologic adjunct or alternative in the therapeutic landscape of BPH. Importantly, its use may be especially advantageous in patients who are unwilling or unable to tolerate conventional medications due to side effects, particularly those related to sexual function.

Moving forward, these preliminary findings underscore the need for randomized, double-blind, placebo-controlled trials involving larger patient cohorts and longer follow-up durations. Such studies should incorporate not only symptom scores and urodynamic parameters but also objective biomarkers of inflammation, prostate volume changes, and detailed sexual function domains. Stratification by baseline sexual function status and symptom severity could also help delineate which subgroups stand to benefit most from *Xipag*® therapy.

Conclusions

In this preliminary investigation, *Xipag*® demonstrated promising efficacy in improving QoL and patient-reported outcomes in men with BPH, without compromising sexual or ejaculatory function. Secondary benefits included improved urinary flow and reduced LUTS severity. These findings support the potential role of *Xipag*® as a non-pharmacologic adjunct or alternative in BPH management. Further controlled studies are necessary to establish its long-term safety and therapeutic value.

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Declarations

Ethical approval and consent for participate: *This prospective, single-arm observational study was conducted in accordance with the ethical standards of the Declaration of Helsinki and was approved by the institutional Ethics Committee (STS CE Lazio1/N-945, "Lazio 1", San Camillo Forlanini Hospital, Rome, Italy). Written informed consent was obtained from all participants.*

Availability of data and material: *The data that support the findings of this study are available from the corresponding author, [VI], upon reasonable request.*

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

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Authors' contributions: *Matteo Vittori conceived the study, conducted the literature review and collected the data; Valerio Iacovelli conceived the study, wrote the manuscript; Marco Carilli conceived the study, wrote the manuscript; Carlo Brocca reviewed the manuscript; Filomena Petta collected the data, interpreted the results; Beatrice Filippi performed the statistical analysis; Giulia Di Giovanni performed the statistical analysis; Marta Signoretti collected the data; Francesco Maiorino collected the data; Michele Antonucci collected the data; Andrea Benedetto Galosi reviewed and edited; Pierluigi Bove conceived the study, wrote the manuscript, reviewed and edited.*

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