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Safety and efficacy of LibidUp-PE supplement on premature ejaculation: A randomized, placebo-controlled double-blind, crossover study

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ABSTRACT

Premature ejaculation (PE) is the most common male sexual dysfunction. Selective serotonin reuptake inhibitors (SSRIs) are currently recommended for PE. However, the side effects of SSRIs, such as nausea, vomiting, and xerostomia, pose challenges to clinicians. Simultaneously, evidence indicates that psychological and behavioral treatments are often insufficient. LibidUp-PE is a nutraceutical designed to enhance sexual wellness and contains a combination of essential amino acids to boost stamina and vigor, addressing concerns like erectile dysfunction (ED). This study aimed to assess the safety and efficacy of LibidUp-PE in the treatment of PE. In this crossover, double-blind, placebo-controlled trial, 76 patients with PE were randomly divided into two groups. Group A received LibidUp-PE, whereas Group B received a placebo for 12 weeks. Following a 2-week wash-out period, the groups switched treatments for another 12 weeks. Intravaginal ejaculatory latency time (IELT) and post-ejaculatory refractory time (PERT) were measured as the primary outcomes to evaluate PE improvement. Plasma serotonin levels were measured as secondary parameters using enzyme-linked immunosorbent assay. The results showed that LibidUp-PE significantly improved the IELT score, increasing from 0.8 ± 0.2 min to 2.9 ± 1.1 min ($p < 0.01$). PERT scores also significantly decreased from 15.8 ± 1.7 min to 5.6 ± 0.6 min after 12 weeks of LibidUp-PE treatment. Plasma serotonin levels significant increased from 93.6 ± 7.8 ng/mL to 168.4 ± 12.8 ng/mL ($p < 0.001$) with LibidUp-PE treatment. In contrast, no significant improvements were observed in the placebo group. Notably, none of the participants withdrew their consent due to adverse reactions, which is indicative of the safety and tolerability of LibidUp-PE. In conclusion, 12-week treatment with LibidUp-PE demonstrated a beneficial effect in reducing PE symptoms, as reflected by improved IELT, reduced PERT, and increased plasma serotonin levels. Therefore, LibidUp-PE could be a promising solution for individuals with PE.

1. Introduction

Untimely discharge (premature ejaculation, PE) is possibly the most common form of male sexual grievance [1]. Approximately 20–30% of men experience PE eventually throughout their lives [2], underscoring its prevalence and the need for effective treatments. Medicines for PE medications predominantly include pharmacological and mental and social therapies [3]. The World Health Organization (WHO) Second International Consultation on Sexual Health characterized it as "Persistent or recurrent ejaculation with minimal stimulation before, on, or shortly after penetration and before the person desires, over which the person has little or no voluntary control, causing annoyance or distress to the person and/or his sexual partner" [4]. This multivariate definition incorporates the following primary components of PE: ejaculatory dormancy, control, and sexual fulfilment [5].

Conventional treatments for PE predominantly involve pharmacological and psychological or behavioral interventions. Among the pharmaceutical options, oral 5-HT receptor reuptake inhibitors (SSRIs) like fluoxetine, paroxetine, sertraline, and dapoxetine have shown effectiveness in extending ejaculation latency [6,7]. However, these medications come with a set of side effects, including nausea, vomiting, and

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List of abbreviations

PE	Premature Ejaculation
SSRIs	Selective Serotonin Reuptake Inhibitors
IELT	Intravaginal Ejaculatory Latency Time
PERT	Post-Ejaculatory Refractory Time
ED	Erectile Dysfunction
ELISA	Enzyme-Linked Immunosorbent Assay
WHO	World Health Organization
5-HT	5-Hydroxytryptamine (Serotonin)
PDE5	Phosphodiesterase Type 5
SPSS	Statistical Package for the Social Sciences
SD	Standard Deviation
GSE	Grape Seed Extract

xerostomia, which can be challenging for both patients and healthcare providers [8]. Psychological and behavioral therapies, considered a part of the treatment spectrum, are limited in their efficacies [9], giving rise to the exploration of alternative approaches.

LibidUp-PE, a nutraceutical aimed at promoting sexual well-being, has recently gained attention. By combining a blend of L-arginine, grape seed extract (GSE), safed musli, inositol, L-tryptophan, and vitamin B6, we aimed to address the multifaceted nature of PE by enhancing stamina and vigor, igniting sexual desire, and regulating the ejaculatory cycle. The primary objective of this study was to evaluate the safety and efficacy of LibidUp-PE in managing PE, with the potential to provide an alternative to existing treatments.

These findings provide promising insights into the potential of LibidUp-PE as an alternative treatment for PE. The observed improvements in the intravaginal ejaculatory latency time (IELT), post-ejaculatory refractory time (PERT), and plasma serotonin levels after 12 weeks of treatment suggest that this nutraceutical could offer a valuable solution for individuals with PE. This study underscores the importance of exploring innovative approaches to address sexual wellness concerns and the potential for nutraceutical interventions to provide safe and effective alternatives for individuals seeking relief from premature ejaculation.

2. Material and methods

2.1. Study design

This single-center, randomized, double-blind, placebo-controlled, crossover design study was conducted at the Department of Urology, SRM Medical College Hospital and Research Centre, Kattankulathur, Tamil Nadu, India. This study was conducted in accordance with the standards of the International Committee on Harmonization of Good Clinical Practice and the revised Declaration of Helsinki. The Institutional Human Ethics Committee approved the study protocol (Permission No: 2366/IEC/2021), and the study was registered in the Clinical Trial Registry of India (Registration No: CTRI/2021/10/037471). Written informed consent was obtained from all participants.

2.2. Study criteria

Inclusion Criteria: 21–65-year-old participants with a baseline IELT of <2 min and who had met diagnostic criteria for premature ejaculation profile (PEP score ≤ 11) were eligible for this study.

Exclusion Criteria: Participants with ED (separate or in addition to PE) or who were using sildenafil or other drugs belonging to the PDE5 inhibitor family, depression, and/or the use of selective serotonin reuptake inhibitors, tricyclic antidepressants, etc., which could have affected the study outcomes, were excluded from the study.

2.3. Study procedure

A clinical trial was designed to evaluate the efficacy and safety of the investigational product LibidUp-PE (10 g) in the treatment of participants with PE for 12 weeks. Participants were enrolled in a 1:1 ratio into either the LibidUp-PE or placebo group after screening and signing informed consent. After 2 weeks of the washout period, the subjects were crossed over to placebo or Libidup-PE for an additional 12 weeks. Serum 5-HT levels, IELT, and PERT were estimated at baseline (before treatment) and after treatment to determine the efficacy of LibidUp-PE in PE.

IELT is a vital parameter in the evaluation of the effectiveness of PE treatments and is an objective prospective measurement using a stopwatch operated by a female partner [10]. The IELT questionnaire, which is used to determine the time taken to ejaculate after vaginal penetration using a stopwatch, was used to determine the latency time as the primary efficacy endpoint to evaluate the treatment effect. It was measured at the screening visit and after 12 weeks of treatment, and the change from baseline to the end of the study period was evaluated.

The secondary endpoint was PERT that is defined as the time to re-attain erection after an ejaculation, which was measured by asking each participant to attempt a second sexual intercourse after the first. PERT was also measured by either partner using the stopwatch technique.

Blood samples (3 mL) were drawn from the antecubital veins of all participants, centrifuged at 4000 rpm for 5 min, and stored at -20°C until further analysis. Quantitative Sandwich ELISA using a microplate reader (Thermo Scientific Multiscan) was used to quantitatively determine serotonin, and the results were reported in nanograms per milliliter. Serotonin was estimated according to the instruction of KIT (Cat. MBS039395-96).

2.4. Statistical analysis

Statistical analyses were performed using SPSS version 16.0. Descriptive statistics were used to summarize the demographic and baseline characteristics. Data are presented as mean $\pm$ SD. An unpaired *t*-test was used to compare IELT, PERT, and plasma serotonin levels between the groups. All results were considered statistically significant at $p < 0.05$.

3. Results

A total of 115 subjects were assessed for eligibility, in which 39 subjects were excluded because of unwillingness and not having met the inclusion criteria. The remaining 76 participants were randomized into two groups. Groups A and B received LibidUp-PE and Placebo, respectively, for 12 weeks, followed by a cross over after 2 weeks of washout period (Fig. 1).

Baseline demographic details are shown in Table 1.

3.1. IELT improvement with LibidUp-PE treatment

To measure the changes in IELT after LibidUp-PE treatment, baseline IELT was established in participants of both the groups. IELT was reassessed after 12 weeks of treatment with a crossover of patients from placebo to LibidUp-PE. Baseline (geometric mean $\pm$ SD) IELT for patients randomized to LibidUp-PE or placebo was 0.8 ± 0.2 min and 0.9 ± 0.4 min, respectively. At the end of the first 12 weeks of treatment, IELT increased from 0.8 ± 0.2 min to 2.9 ± 1.1 min ($p < 0.01$) with LibidUp-PE and from 0.9 ± 0.4 min to 1.0 ± 0.9 min (ns) with placebo. At the time of the next 12 weeks of follow-up, patients who crossed over from placebo to LibidUp-PE reported significant improvements in IELT (from 1.0 ± 0.9 min to 2.4 ± 0.5 min, $p < 0.05$), whereas in the other arm, a significant reduction in IELT was found compared with the end of study (from 2.9 ± 1.1 min to 1.4 ± 1.2 min, $p < 0.05$) (Fig. 2).

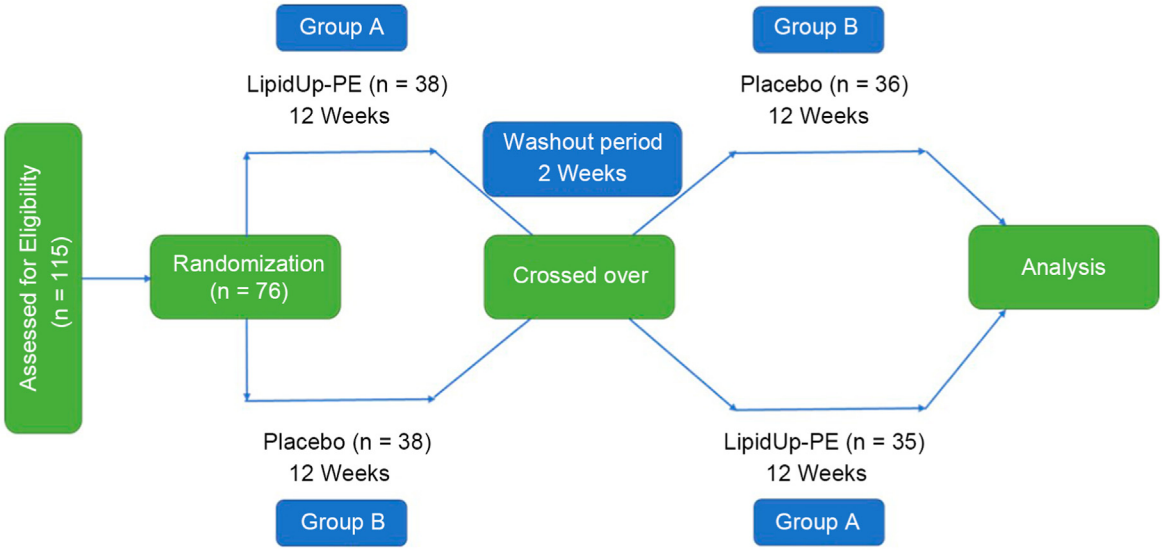

Fig. 1. CONSORT flow diagram.

Table 1
Baseline demographics details.

Group	LibidUP-PE	Placebo	P Value
Demographic Characteristics			
Age (y)	32.6 ± 3.8	31.1 ± 4.2	0.69
Height (cm)	170.2 ± 5.9	172.4 ± 5.2	0.72
Weight (kg)	67.2 ± 6.3	66.5 ± 7.2	0.92
BMI (kg/m^2)	23.6 ± 1.2	22.9 ± 1.6	0.47
Course of disease (y)	4.2 ± 2.8	4.3 ± 2.2	0.93
IELT (min)	0.8 ± 0.2	0.9 ± 0.4	0.88
PERT (min)	15.8 ± 1.7	16.3 ± 1.2	0.36
Serotonin (ng/mL)	93.6 ± 7.8	98.8 ± 6.2	0.24

Values are expressed as mean ± SD, Level of Significance: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$.
BMI, Body mass index; IELT, Intravaginal ejaculation latency time; PERT, Post-ejaculation refractory time.

3.2. PERT enhancement with LibidUp-PE treatment

To examine the effects of LibidUp-PE on PERT, baseline PERT data were collected from participants receiving LibidUp-PE and the placebo. PERT was reassessed after 12 weeks of the treatment with a crossover of patients from placebo to LibidUp-PE. Compared with the placebo, LibidUp-PE significantly ($p < 0.001$) decreased the PERT (15.8 ± 1.7 min to 5.6 ± 0.6 min) after 12 weeks of treatment. At the time of follow-up, patients who crossed over from placebo to LibidUp-PE reported significant improvements in PERT (from 15.0 ± 0.8 min to 5.2 ± 1.1 min, $p < 0.001$), whereas in the other arm, a significant increase in PERT was observed compared with the end of study (from 5.6 ± 0.6 min to 13.1 ± 1.5 min, $p < 0.001$). (Fig. 3).

3.3. Alterations in plasma serotonin levels

To investigate the changes in plasma serotonin levels resulting from LibidUp-PE treatment, baseline plasma serotonin levels were measured in patients in both the LibidUp-PE and placebo groups. Plasma serotonin levels were reassessed after 12 weeks of treatment, with a crossover of patients from placebo to LibidUp-PE. Baseline plasma serotonin levels for the patients in the LibidUp-PE or placebo group were 93.6 ± 7.8 ng/mL and 98.8 ± 6.2 ng/mL, respectively. Plasma serotonin levels significantly

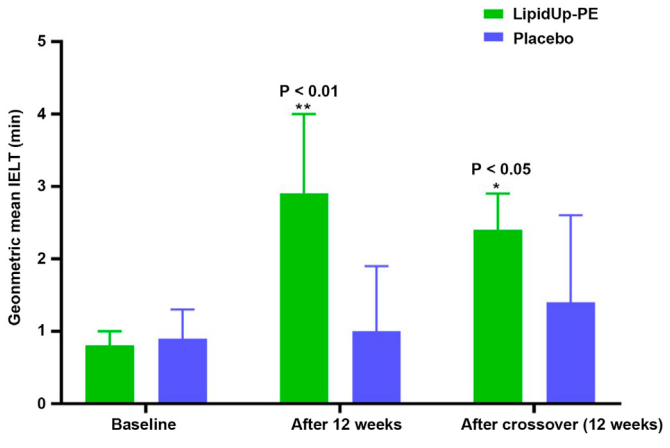

Fig. 2. Comparing the effect of LibidUp-PE and Placebo on intravaginal ejaculatory latency time in patients with premature ejaculation (Values are expressed as Geometric mean ± SD, Level of Significance: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

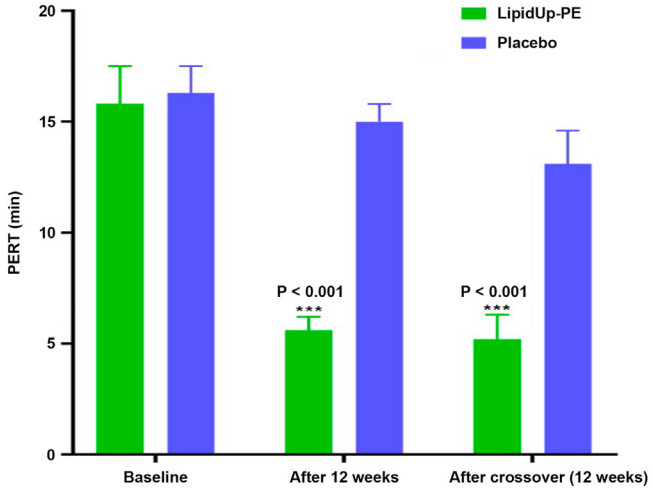

Fig. 3. Comparing the effect of LibidUp-PE and Placebo on post-ejaculatory refractory time in patients with premature ejaculation (Values are expressed as mean ± SD, Level of Significance: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

elevated from 93.6 ± 7.8 ng/mL to 168.4 ± 12.8 ng/mL ($p < 0.001$) with LibidUp-PE treatment after 12 weeks. After crossing over from placebo to LibidUp-PE, plasma serotonin levels increased significantly from 124.6 ± 8.8 ng/mL to 172.3 ± 9.7 ng/mL ($p < 0.01$), but in the case of placebo, no significance was observed (Fig. 4).

3.4. Adverse events and safety profile

Patients were systematically questioned during each session regarding adverse events during LibidUp-PE or Placebo treatments. During treatment, three patients reported diarrhea and two reported mild headache; however, no patient had withdrawn from the study due to adverse drug events. The reported adverse drug events were adequately addressed by a physician.

4. Discussion

In recent years, PE has become the most frequent sexual grievance among the male population [11]. Some well-known SSRIs have adverse effects [6]. LibidUp-PE is a nutraceutical containing L-arginine and GSE, which can enhance the sexual well-being of individuals. This randomized, placebo-controlled, double-blind, crossover study was conducted to evaluate the safety and efficacy of LibidUp-PE on premature ejaculation. In total, the study was performed with 72 samples. A 12-week study was conducted with 4 weeks of baseline assessment. Following a 2-week washout period, the participants were crossed over for another 12 weeks. Blood serotonin, IELT, and PERT levels were calculated. IELT revealed a substantial increase with LibidUp-PE compared to the placebo, according to the study's primary findings. Surprisingly, at the end of the study period, LibidUp-PE significantly improved in PERT. Furthermore, following a 12-week treatment cycle, LibidUp-PE therapy significantly increased plasma serotonin levels.

IELT was timed on a stopwatch from 'start' (penetration) to 'stop' (ejaculation). The stopwatch could be handled by either pair; however, it was desired that the same person be in charge of every IELT measurement for the length of the study and that they record the time accurately [12]. They were given the task of calculating and recording their exact ejaculation time. IELT was performed before and after the treatment for a total of 12 weeks. Kaynar et al. reported similar findings regarding tramadol use. Compared with placebo, after 8 weeks of treatment of PE with tramadol, a significant increase in mean IELT was noted.

PERT, or the time to re-attain an erection after ejaculation, was the secondary endpoint that was measured by each participant attempting to successively engage in a second sexual intercourse. During each session, the participants were asked a series of questions about the adverse events they experienced during LibidUp-PE or Placebo treatments. Three participants experienced diarrhea and two had moderate headaches throughout the course of therapy, but none withdrew participation from the trial due to the adverse effects. The reported adverse events were carefully managed under the supervision of a physician. Our study reported a positive impact on PE in men. Based on our results, the investigational product is a safe and effective treatment.

The limitations of this study include the small sample size of only 72 participants, which may not be representative of the broader male population with PE. Larger sample sizes would provide more robust and generalizable results. Additionally, this study had a relatively short treatment period of 12 weeks. PE can be a chronic condition, and its long-term effects and safety profiles may not have been fully assessed in this study. Furthermore, the study primarily focused on the 12-week treatment period and did not provide information on the potential long-term effects or relapse rates after discontinuing LibidUp-PE therapy.

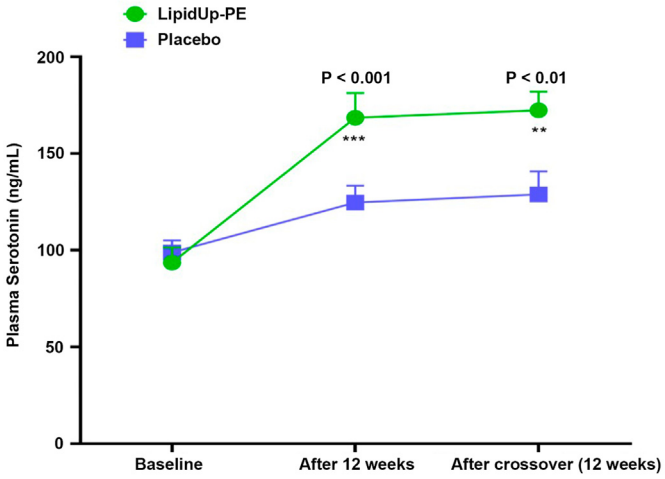

Fig. 4. Comparing the effect of LibidUp-PE and Placebo on plasma serotonin in participants with premature ejaculation (Values are expressed as mean ± SD, Level of Significance: *, $p < 0.05$; **, $p < 0.01$; ***, $p < 0.001$).

5. Conclusion

In conclusion, this randomized crossover study implies that LibidUp-PE supplementation increases IELT and reduces PERT in participants with PE. Plasma serotonin levels also increased significantly in the LibidUp-PE treatment group, highlighting the potential pharmacological mechanisms underlying the beneficial effects of LibidUp-PE and offering promising prospects for the management of PE.

Author contributions

Thangavel Mahalingam Vijayakumar: conception, study design, writing, review and editing. Jagadeesan M: data collection, experimentation, review and editing. Adhisaya A: data collection, experimentation and writing. Rajappan Chandra Satish Kumar: data collection and experimentation. Srinivasan T: data analysis and interpretation. Alphienes Stanley Xavier: data analysis and interpretation. Pavithra Anandan: data analysis and interpretation. All the authors have read and approved the final manuscript.

Data availability

Data will be made available on reasonable request.

Ethics approval

The Institutional Human Ethics Committee approved the study protocol (Permission No. 2366/IEC/2021). Written informed consent was obtained from all study participants prior to enrollment. The study was registered in the Clinical Trial Registry of India (Registration No: CTRI/2021/10/037471).

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Conflict of interest exists with the company (MMC Pharmaceuticals Ltd)

that may benefit from the results of the study.

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