

A combination of tryptophan, *Satureja montana*, *Tribulus terrestris*, *Phyllanthus emblica* extracts is able to improve sexual quality of life in patient with premature ejaculation

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Summary *Objective: The management of patient affected by premature ejaculation (PE) is nowadays not highly satisfactory. Here, we aimed to evaluate the tolerability and efficacy of a combination of tryptophan, *Satureja montana*, *Tribulus terrestris*, *Phyllanthus emblica* extracts in order to improve sexual quality of life in patients with premature ejaculation.*

*Materials and methods: All patients attending to 5 urological centers from January 2015 to March 2015, due to premature ejaculation were enrolled in this study. At the enrolment visit, all subjects underwent self-administered IIEF-5, Male Sexual Health Questionnaire-Ejaculation Disorder (MSHQ-EJD), PEDT and IELTS (calculated as mean from that perceived by partner and that perceived by patient) and underwent urological visit and laboratory examinations. All patients received one tablet per day of a combination of tryptophan, *Satureja montana*, *Tribulus terrestris*, *Phyllanthus emblica* extracts for 3 months (Group A). After 3 months all patients underwent follow-up visit with the same investigations that have been carried out in the enrolment visit. The results were compared with a cohort of patients enrolled in the same period in another urological center and considered as a control group (Group B). All patients in the control group underwent counseling and sexual behavioral treatment without any pharmacological compound.*

Results: At the follow-up analysis, significant changes in terms of IELT in the Group A (mean difference: 31.90; $p < 0.05$) at 3 months and versus Group B at the intergroup analysis (mean difference: 30.30; $p < 0.05$) were reported. In the group A, significant differences from baseline to last follow-up were observed relative to IIEF-5 (mean difference: 1.04; $p < 0.05$), PEDT (mean difference: -2.57; $p < 0.05$) and FSH (mean difference: -16.46; $p < 0.05$).

*Conclusion: In conclusion, patients affected by PE may significantly benefit from oral therapy with a combination of tryptophan, *Satureja montana*, *Tribulus terrestris*, *Phyllanthus emblica* extracts in terms of IELT and PEDT scores improvement.*

KEY WORDS: Premature ejaculation; Erectile dysfunction; Tryptophan; *Satureja montana*; *Tribulus terrestris*; *Phyllanthus emblica*.

Submitted 9 November 2015; Accepted 4 December 2015

No conflict of interest declared.

INTRODUCTION

Over the past 30 years, the premature ejaculation (PE) treatment paradigm, which previously limited to behavioral psychotherapy, has expanded to include drug treatment (1). Dapoxetine (Priligy, Johnson & Johnson, New Brunswick, NJ) is the first and the only product licensed for the treatment of PE in men aged 18-64 years, and it belongs to a class of drugs called selective serotonin reuptake inhibitors (SSRIs), which are frequently used to treat depression (2-4). Across trials, receiving dapoxetine 30 and 60 mg were well tolerated with a low incidence of adverse events (AEs) (2). The most common AEs were those typically accompanied with SSRIs agents, and the symptoms were mild (2). Furthermore, although treatment with marketed SSRIs had been associated with sexual dysfunctions and suicide attempts, there were no reports on sexual dysfunctions or suicide events as well as suicide attempts in these 5 RCTs (5-6). However, there were limited available data about using dapoxetine for a long time. Phytotherapeutics should be an interesting option because of their generally low side effects and high acceptance by the patients. We focused our attention on some compounds that may be useful for the treatment of PE. Tryptophan is an interesting phytotherapeutic compound. 5-Hydroxytryptophan (5-HTP) is the intermediate metabolite of the essential amino acid L-tryptophan in the biosynthesis of serotonin (7-8). The role of serotonin in the ejaculation control is well known and the well demonstrated (9-10). Moreover, 5-HTP is well absorbed from an oral dose, with about 70% was found in the bloodstream (11). Furthermore, 5-HT showed a good pharmacological profile with good efficacy and appeared to be better tolerated than SSRIs (12). On the other hand, *Satureja montana* (winter savory) is a medicinal plant traditionally used to treat different disorders including male sexual dysfunction (13). Recently, *Zavatti et al.* found that *Satureja montana* is able to delay ejaculation latency without exerting any negative effect on the other parameters of sexual behavior and without exerting a sedative effect (13). Finally, the role of *Phyllanthus emblica*. *Chebularic*

acid, the major constituent of *Phyllanthus emblica*, is a benzopyran tannin compound with various kinds of medicinal potentials including improvement of male sexual dysfunction (14-15). In fact, Chebulagic acid is able to inhibit Rho-kinase 2 and may be useful in management of erectile dysfunction (14). Here, we aim to evaluate the tolerability and efficacy of a combination of tryptophan, *Satureja montana*, *Tribulus terrestris*, *Phyllanthus emblica* extracts (EIACUMEV®) in order to improve sexual quality of life in patients with premature ejaculation.

PATIENTS AND METHODS

Study design

All patients attending to 5 urological centers from January 2015 to March 2015, due to premature ejaculation were enrolled in this study. At the enrolment visit, all subjects underwent self-administered IIEF-5, Male Sexual Health Questionnaire-Ejaculation Disorder (MSHQ-EjD), PEDT and IELTS and underwent urological visit and laboratory examinations. The IELT has been calculated as mean from that perceived by partner (PIELT) and that perceived by patient (IELT). All patients underwent preliminary assessment including a detailed medical and sexual history to evaluate the presence of underlined risk factors such as infections or diabetes mellitus. All patients received one tablet per day of a combination of tryptophan, *Satureja montana*, *Tribulus terrestris*, *Phyllanthus emblica* extracts for 3 months (Group A). After 3 months all patients underwent follow-up visit with the same investigations that have been carried out in the enrolment visit. The results were compared with a cohort of patients enrolled in the same period in another urological center and considered as a control group (Group B). All patients in the control group underwent counseling and sexual behavioral treatment without any pharmacological compound. All subjects gave written informed consent before entering the study, which was conducted in accordance with the Declaration of Helsinki.

Inclusion and exclusion criteria

The primary inclusion criteria were age ≥ 18 years of age and in a stable monogamous relationship for ≥ 6 months

were eligible if they met the DSM-IV-TR criteria for PE for ≥ 6 months, indicated at least moderate PE-related distress or interpersonal difficulty, and reported an IELT of ≤ 2 min in ≥ 75% of evaluable events during a 4-wk screening/baseline period. Exclusion criteria were as follows: any medical treatment for sexual dysfunction before or during the study, congenital or acquired penile curvature or chordee with hypospadias, age > 75 years, hypogonadism (total testosterone level < 8 nmol or serum testosterone in the range of 8-11 nM and free testosterone < 220 pmol, assessed at least on two occasions). To be able to exclude organic sexual dysfunctions and other underlying illnesses, fasting blood glucose level, urinalysis, complete blood count, sex hormones, and prolactin levels were measured. All measurements were conducted by a single physician unaware of the treatment status. Moreover, all patients with erectile dysfunction (a reported IIEF-15-EFD score ≤ 21) were excluded, as suggested by *Salonia* (16).

Questionnaires and urological examinations

Sexual health was evaluated using available validated instruments for the study of erectile function (International Index of Erectile Function-15 erectile function domain [IIEF-15-EFD]) (17) and ejaculatory status (PEDT) (18). In order to exclude all patients with lifelong PE, a careful urological visit with disease history collection has been performed at the arrival at each Centre, as suggested by *Jannini et al.* (19). Moreover, the Male Sexual Health Questionnaire-Ejaculation Disorder (MSHQ-EjD) was also used to evaluate the ejaculation function (20).

Assignment to the groups

All patients were assigned to each group on the basis of the attending center. All patients attending to 5 centers (Rome 2 centers, Catania, Florence, Catanzaro) were assigned to Group A, while all patients attending another center (Trento) were assigned to Group B (controls). The study design is displayed in Figure 1.

Group A

The first group received one tablet orally a day for 3 months and one tablet consisted of 300 mg of *Satureya*

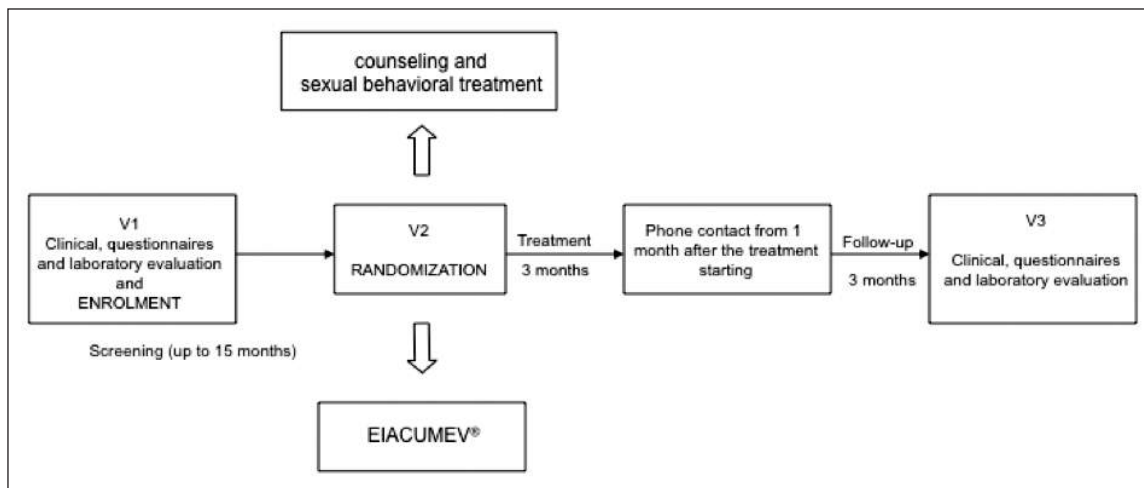


Figure 1.
The figure shows the study design schedule.

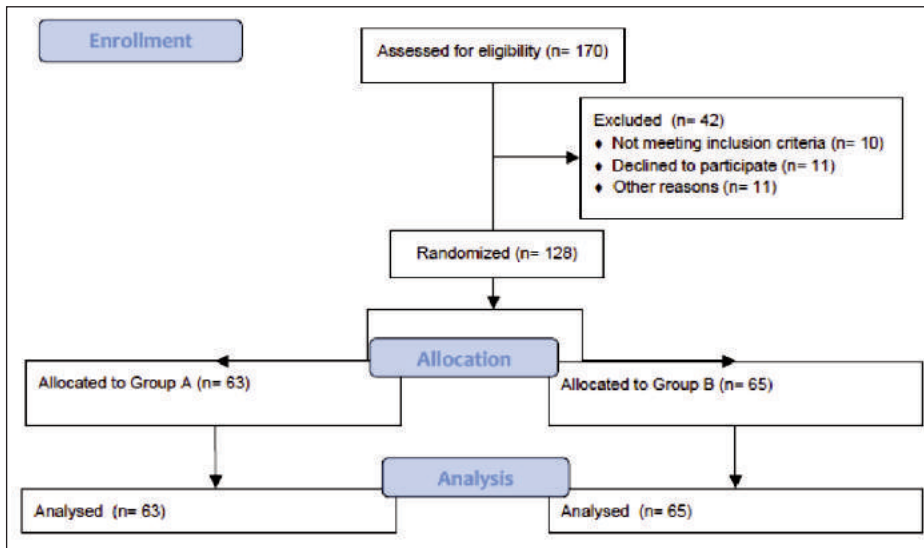


Figure 2.
The figure shows the study flow chart in accordance to the CONSORT guidelines.

montana, *Tribulus terrestris*, *Phyllanthus emblica*, Cardamomo, L-tryptophan, ascorbic acid, vitamin PP, vitamin B1, vitamin B6 (*EiacuMev*[®], *Farmaceutica MEV, Siena, Italy*). We monitored adverse events on the light of common terminology criteria for adverse events (CTCAE) guidelines. Safety assessments included treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and orthostatic vital signs (blood pressure and heart rate).

Group B

All patients in the control group underwent counseling and sexual behavioral treatment without any pharmacological compound. The counseling and sexual behavioral treatment has been carried out in collaboration with a dedicated psychologist, as commonly in our routinely clinical practice. The sexual counseling and psychotherapy has been performed in line with the suggestions of Rowland and Cooper (21).

Main outcome measures

The primary end point was stopwatch-measured IELT (held by the partner), reported for each intercourse episode. Secondary outcomes were the change from baseline to end point of MSHQ-EJD, IIEF-5 and PEDT.

Statistical analysis and study population

As null hypothesis, we assumed there would be no difference in terms of mean IELT score, between the two groups. A sample size of 60 subjects per treatment group provided 90% power (two-sided $\alpha = 0.05$), to detect a 30 seconds difference in mean IELT between patients and controls. The maximum sample size was set to 70 subjects per group, allowing for a 15% dropout rate. At baseline, the independent sample 2-tailed t-test was used to compare variables. For categorical parameters, chi-square test was applied. Changes from baseline to end of therapy were analyzed using ranked one-way analysis of variance (ANOVA) with a term for treatment group. Data were reported as means \pm standard deviation (SD). For all statistical comparisons, significance was considered as $p < 0.05$. All reported p-values are two-sided. All

statistical analyses were performed by using SPSS 11.0 for Apple-Macintosh (SPSS, Inc., Chicago, Illinois).

RESULTS

One hundred and seventy patients were enrolled. Forty-two patients were excluded and 128 patients were finally randomized, 63 and 65 subjects in the group A and in the group B completed the study protocol. The flow chart of this study is presented in Figure 2.

Baseline characteristics

All anamnestic, clinical, and questionnaires characteristics of all enrolled patient are displayed in Table 1.

Table 1.
Baseline characteristics of patients enrolled.

	Group A	Group B
No. of patients	63	65
Age (yr), mean \pm SD	32.03 \pm 8.68	35.37 \pm 8.81
BMI (Kg/m ²), mean \pm SD	26.36 \pm 3.0	25.2 \pm 3.5
LH, mean \pm SD	87.96 \pm 56.92	86.76 \pm 55.43
FSH, mean \pm SD	57.00 \pm 37.29	54.61 \pm 35.70
Total testosterone, mean	6.89 \pm 3.87	7.01 \pm 3.02
Smoking habit, n (%)	25 (39.68)	26 (36.92)
IIEF-5, mean \pm SD	27.31 \pm 2.86	27.71 \pm 3.77
PEDT, mean \pm SD	13.82 \pm 2.79	14.05 \pm 2.54
IELT (sec), mean \pm SD	54 \pm 17.76	52 \pm 18.82
EjQ, mean \pm SD	14.89 \pm 1.07	15.01 \pm 1.35
PSV, mean \pm SD	31.52 \pm 6.60	30.02 \pm 5.56
EDV, mean \pm SD	1.5 \pm 1.0	1.2 \pm 2.0

BMI = Body Mass Index; IIEF-EF = International Index of Erectile Function-Erectile Function; IIEF-IS = International Index of Erectile Function-Intercourse Satisfaction; IIEF-OF = International Index of Erectile Function-Orgasmic Function; IIEF-SD = International Index of Erectile Function-Sexual Desire; IIEF-OS = International Index of Erectile Function-Overall Satisfaction; MSHS-EJD = Male Sexual Health Questionnaire-Ejaculation Disorder; SQoL-M = Sexual Quality of life instrument for Men; PSV = peak systolic velocity; EDV = end diastolic velocity.

Table 2.
Mean changes from baseline to 3 months for primary and secondary outcomes.

	Group A	Group B
LH, mean ± SD	12.72 ± 60.07	10.50 ± 55.00
FSH, mean ± SD	-16.46 ± 37.42 ^{a, b}	2.52 ± 5.76
Total testosterone, mean	1.55 ± 10.93	1.23 ± 9.81
IIEF-5, mean ± SD	1.04 ± 1.67 ^a	0.31 ± 0.87
PEDT, mean ± SD	-2.57 ± 2.38 ^{a, b}	-1.03 ± 2.45
IELT (sec), mean ± SD	31.90 ± 45.68 ^{a, b}	1.60 ± 9.81
EJQ, mean ± SD	-0.015 ± 0.65	0.02 ± 0.89

^a p < 0.05 vs. baseline; ^b p < 0.05 vs. Group B.

Follow-up examination

The Table 2 lists the mean change differences from baseline to 3 months relative to main outcome measures. When concerning the primary endpoint of this study, we observed significant changes of the IIELT in the Group A (mean difference: 31.90; p < 0.05) at 3 months and versus Group B at the intergroup analysis (mean difference: 30.30; p < 0.05). In the group A, significant differences from baseline to last follow-up were observed relative to IIEF-5 (mean difference: 1.04; p < 0.05), PEDT (mean difference: -2.57; p < 0.05) and FSH (mean difference: -16.46; p < 0.05). Significant differences were found at the intergroup

analysis when considering previous outcome measures (Table 2; Figure 3).

When considering serum TT and MSH-EjD, both groups did not show any difference after 3 months.

Adverse events

All subjects included in the study protocol, tolerated the treatments and none reported adverse events.

DISCUSSION

Even if PE is one of the most common sexual dysfunctions among young male patients and in spite of the increasing interest in PE in the field of sexual medicine, a highly satisfactory treatment in terms of efficacy and safety is still needing (22). For these reasons, even if the preferred management of PE is on-demand Dapoxetine, many urologists used other treatment options in 35% of the initial treatment cases and 50% of the second-line treatment cases (23). Here, we demonstrated that the use of tryptophan, Satureja montana, Tribulus terrestris, Phyllanthus emblica extracts is able to improve the patient's ejaculatory control, with a higher IELT and higher level of quality of life. Moreover, we demonstrated a high level of treatment compliance, probably due to the low frequency of adverse events and the efficacy of the treatment in terms of ejaculatory control improvement. The results of our study are probably due to synergic efficacy of Satureja montana and tryptophan. It is really dif-

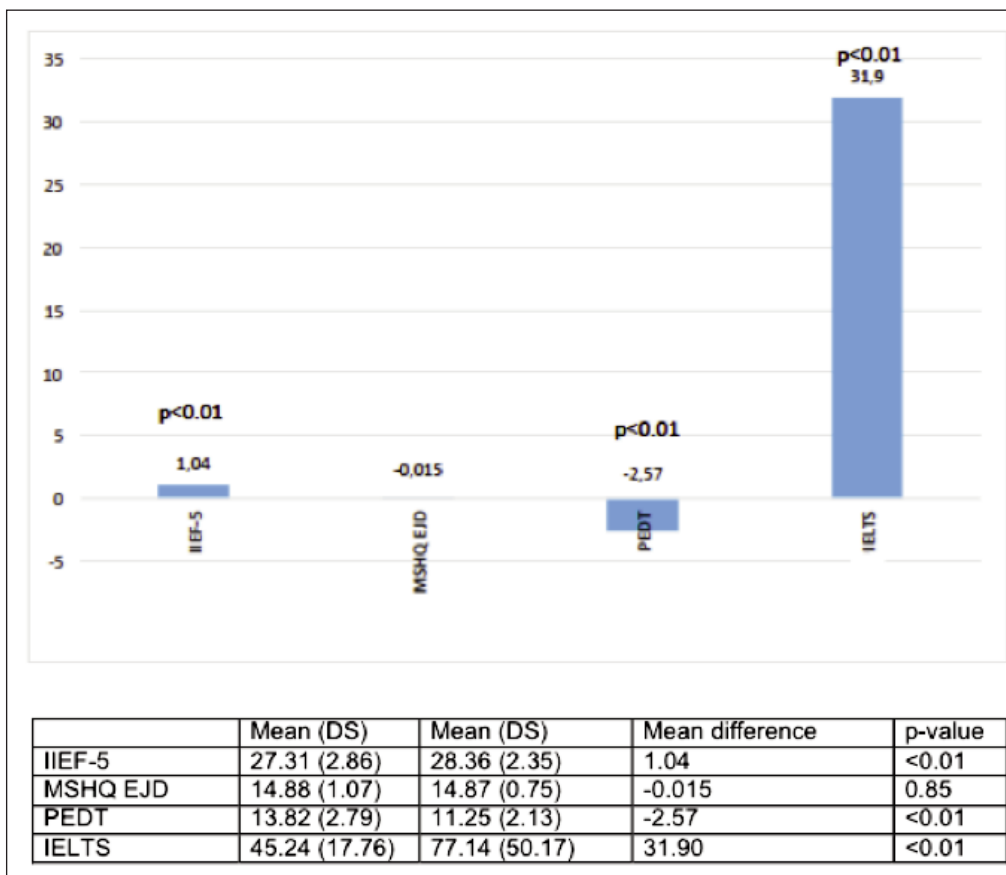


Figure 3.
The figure shows the significant differences found at the intergroup analysis (Group A) when considering outcome measures. VO: enrolment time; V1: follow-up visit (at 3 months from the treatment starting). IIEF-EF = International Index of Erectile Function-Erectile Function; MSHS-EJD = Male Sexual Health Questionnaire-Ejaculation Disorder; PEDT = premature ejaculation diagnostic tool; IELTS = Intravaginal Ejaculatory Latency Time: calculated as mean form partner and patient perceived IELT.

difficult to evaluate the efficacy of each single compound on the PE improvement.

Several Authors demonstrated that serotonin may be associated with physical health as well as mood (24) and, in particular, in healthy people with high trait irritability, tryptophan, relative to placebo, decreased quarrelsome behaviors, increased agreeable behaviors and improved mood (25).

Nonpharmacologic methods of raising brain serotonin may not only improve mood, social functioning of healthy people, but would also improve sexual quality of life, improving the ejaculatory control.

5-hydroxytryptophan is the immediate precursor to serotonin and, by acting on 5-HT1A cerebral autoreceptors, spinal 5-HT1B and 5-HT2C receptors, has a determining role on ejaculation.

On the other hand, *Zavatti et al.* demonstrated that the acute administration of *Satureja montana* extract is able to significantly increase the ejaculation latency and reduced the number of intromissions before ejaculation, without affecting the percentage of animals achieving ejaculation (100% in all experimental groups) (13). They hypothesized that the efficacy of *Satureja montana* on premature ejaculation is due to its impact on male sexual behavior (13). However, even if the plants belonging to the genus *Satureja* are traditionally known as aphrodisiac remedy, no study was performed to confirm this property (13, 26). However, even if our results are promising, this study shows several limitations to take into account.

Firstly, the number of enrolled patients. Even if the number need to treat is correctly calculated is very important to highlight that the safety of phytotherapy should be evaluated with a long-term follow-up, in order to discover delayed adverse side effects. Moreover, the lack of a long-term follow-up in order to evaluate the long-term efficacy of this compound.

CONCLUSION

In our study, we demonstrated that patients affected by PE may significantly benefit from oral therapy with tryptophan, *Satureja montana*, *Tribulus terrestris*, *Phyllanthus emblica* extracts by improving IELT, PEDT and slightly IIEF-5.

ACKNOWLEDGEMENTS

We are grateful to *Professor John Denton (Department of Modern Philology, University of Florence)* for manuscript language revision.

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