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ORIGINAL PAPER

Effect of SA3X (*Spilanthes acmella*) Supplementation on Serum Testosterone Levels in Males with Erectile Dysfunction – A Parallel Double-Blind Randomized Controlled Trial

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ABSTRACT

Objective: *To determine whether SA3X (*Spilanthes acmella*) supplementation improves serum testosterone levels, in comparison with placebo, in participants with erectile dysfunction (ED) and low testosterone levels.*

Materials and methods: *This double-blind placebo-controlled parallel-group was conducted in Hyderabad, India, among male participants who were randomized to SA3X therapy or placebo (1:1) for three months. The change of serum testosterone levels from baseline to months 1, 2, 3 and 6 (three months after completion of the intervention) were assessed using a mixed model repeated measures analysis. Additional secondary outcomes were the change in the Male Sexual Health Questionnaire (MSHQ), International Index of Erectile Function (IIEF) and the duration of penile erection. Stratifying the effect of SA3X on testosterone levels was done to account for potential confounders and effect modifiers. Safety was evaluated.*

Results: *The intention-to-treat population included 215 patients (105 – SA3X therapy; 110 – placebo). SA3X intervention increased the testosterone levels significantly (21.85 vs. 1.89 ng/dL; P<0.001) at the end of month 3. The elevated testosterone levels were maintained at month 6 (18.69 vs. 1.79; P<0.001) even after discontinuation of the intervention. The MSHQ scores, IIEF scores, and duration of penile erection also increased significantly in the SA3X group. Sensitivity analysis showed that the effect of SA3X on testosterone significantly differed by BMI, presence of comorbid conditions and intake of phosphodiesterase-5 inhibitors. Dysgeusia (7.61%) was the significant drug-related adverse effect.*

Conclusion: *Supplementation with SA3X for people with ED and low testosterone is a safe option as it significantly increases testosterone levels along with erectile function.*

Keywords: Spilanthes acmella, erectile dysfunction, serum testosterone, men's health, supplementary therapy, randomized controlled trial.

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INTRODUCTION

Erectile dysfunction (ED) is the inability to either obtain or sustain an erection that is enough for satisfactory sexual performance (1). It affects a significant percentage of males at least periodically. According to the Massachusetts Male Ageing Study (MMAS), the combined prevalence of mild to moderate ED was 52% in males aged 40–70 years. Erectile dysfunction was also strongly associated with age, health status, and emotional function (2). On the other hand, the European Male Ageing Study (EMAS) found that the prevalence of ED increased with age and ranged from 6% to 64% in different age subgroups, with an average prevalence of 30% (3). The medical and socioeconomic effects of ED are substantial due to its high prevalence, significant impact on quality of life, and relationship with diabetes mellitus and cardiovascular disease (4, 5).

Testosterone significantly influences male sexual desire, spontaneous sexual thoughts, sexual drive, receptiveness to erotic stimuli and sexual behaviour (6, 7). It has been hypothesized that in males, normal testosterone concentrations may be required to achieve optimal erectile function because testosterone regulates penile nitric oxide synthase, corporeal venous occlusion, penile blood flow and corpus cavernosum smooth muscle mass in animal models (8-11). Several studies have recommended that males with ED should have their testosterone levels examined and that testosterone supplementation should be explored if levels were low because ED and low testosterone levels frequently coexist (12-16).

Combining testosterone and a phosphodiesterase 5-inhibitor (PDE5-i) has become increasingly common in treating males with ED and low testosterone levels (17, 18). However, adverse effects of the treatment have been profound, and people opt for alternate therapies involving herbal compositions (19, 20). SA3X (*Spilanthes acmella*) has demonstrated significant success in alleviating symptoms of ED (21, 22) and a cross-sectional study has indicated an association with increase in serum testosterone levels (23). Stiriti Ayur Therapies Pvt. Ltd. India has introduced SA3X capsules containing 500 mg of *Spilanthes acmella* extract standardized to 3.5% spilanthol, producing 17.5 mg of spilanthol.

Based on the previous literature regarding the association between testosterone and erectile function, it can be ascertained that testosterone levels impact the functioning of male sexual health. The objective of this trial is to determine whether SA3X supplementation increases serum testosterone levels, compared to placebo, when given to people with ED and low testosterone levels.

MATERIALS AND METHODS

Study design

This randomized placebo-controlled double-blind parallel-group trial with ED participants was approved by the Institutional Ethics Committee – Biomedical Research, Apollo Hospitals, Hyderabad (AHJ-ACD-045/03-21), India, and research was conducted per the Declaration of Helsinki. The study was registered at Clinical Trials Registry India (CTRI/2021/05/033694) in May 2021. Each participant provided a written informed consent. Participant recruitment started in September 2021, and the last patient completed the study in July 2022. Adverse events were reviewed monthly by a data and safety monitoring board. The trial comprised a screening phase, a randomization phase and an intervention phase, in which an optimized dose of SA3X was administered, and the control group received a placebo (multivitamins).

Participants

Participants were recruited through outpatient departments of Apollo Hospitals, Hyderabad, India. Eligibility criteria included age between 35 and 70 years, ED as indicated by a score of 25 or less on the MSHQ (24), a serum total testosterone level less than 300 ng/dL (25), and having a sexual partner. The following exclusion criteria were used: current use of testosterone supplements or immunosuppressants (including, but not limited to, antibiotics, non-steroidal anti-inflammatory drugs, oral/injectable corticosteroids), presence of active urinary tract infection or prostatitis, personality disorder, current or lifetime diagnosis of bipolar disorder, or an eating disorder, history of alcohol or substance abuse disorder (abuse/ dependence) within six months, presence or history of a severe allergic reaction,

unstable cardiovascular, pulmonary, renal, hepatic, endocrine, hematological or active infectious diseases, stroke, cancer, an auto-immune disease. Participants using PDE5-i were asked to stop therapy for one month before enrolment.

Randomization

Participants were randomly assigned without stratification in a concealed 1:1 allocation to either SA3X supplementation or placebo, using permuted blocks with a block size of two, four and six. A randomization sequence was generated by a statistician and provided to the drug pharmacy for implementation. Pharmacists assigned a randomization number to participants and SA3X supplementation or placebo and recorded allocation in a concealed table.

Blinding

Both the investigators and participants were blinded to intervention allocation. SA3X and placebo capsules were packaged in identical containers, and participants were prescribed one capsule daily for three months to maintain blinding. Investigators and study staff did not have access to the randomization table, which the pharmacist sequestered.

Outcome and schedule of assessments

The primary outcome was the change in serum testosterone levels. Serum testosterone was evaluated at baseline, at the end of months 1, 2, 3, and 6 (*i.e.*, three months following completion of the intervention). Serum testosterone levels were measured between 7:00 and 11:00 a.m. using a liquid chromatography-tandem mass spectrometry assay certified by the Indian Council of Medical Research (ICMR). Sensitivity was 2 ng/ dL. Inter-assay coefficient of variation was 7.9% at 48.6 ng/dL, 7.7% at 241 ng/dL, and 4.4% at 532 ng/dL. The bias in quality control samples, provided by the ICMR, between 100 ng/dL and 1000 ng/dL, was less than 6.2%.

Secondary outcomes comprised changes in the MSHQ score, IIEF score and the duration of penile erection. The MSHQ is a 25-item self-administered questionnaire, which encompasses three scales – the Erection scale (three items), the Ejaculation scale (seven items), the Satisfaction scale (six items) – and nine additional items addressing sexual activity, time since last sexual encounter, level, and changes in sexual activity, and bother associated with sexual dysfunction. The total score ranges from 7 to 80 for the three scales of 16 questions, and higher scores indicate better sexual function (24). International Index of Erectile Function is a 15-question validated multi-dimensional self-administered questionnaire that has been found useful in the clinical evaluation of ED and treatment outcomes in clinical trials.; each of the 15 questions receives a score between 0 and 5, which look at the five main areas of male sexual function: erectile function (six items), orgasmic function (two items), sexual desire (two items), intercourse satisfaction (three items) and overall satisfaction (two items) (26-28). Participants were also asked to report the number of minutes they could maintain a penile erection during the initial instance of sexual arousal over the previous seven days without becoming flaccid. The average duration was calculated at baseline and all subsequent follow-ups.

Sample size determination

We hypothesized that the SA3X supplementation would improve the serum testosterone by 10 points. A sample size of 85 evaluable participants in each group would provide approximately 80% power to detect a clinically meaningful 10-point difference in serum testosterone levels between the placebo and SA3X groups in an unadjusted linear regression model. In anticipation of an attrition rate of less than 20%, the sample size was increased to 106 in each group.

Statistical analysis

The change from baseline in serum testosterone was analyzed using a mixed model repeated measures (MMRM) technique. It was also used to compare the secondary outcomes, *i.e.*, change from baseline in the total MSHQ score, scores on the IIEF, and duration of penile erection. Sensitivity analyses were done using conventional linear and logistic regression. Subsequently, exploratory models were employed to assess whether the inclusion of covariates already described as either potential confounders or effect modifiers affected the estimates and whether results differed within specific sample subgroups (for example, among participants with diabetes or testosterone levels less than 250 ng/dL). These exploratory subgroup models were not pre-specified. Finally, Chi-square or Fisher exact tests

were used to compare the number and percentage of participants in each group who reported adverse events. All point estimates had 95% confidence intervals (CIs), and all hypothesis tests were two-sided. The null hypothesis could only be rejected at the 0.05 level for results to be deemed statistically significant. Statistical analyses were done in IBM SPSS Statistics for Windows, version 26 (IBM Corp., Armonk, NY, USA).

RESULTS

Participants

After screening 461 male participants, 215 subjects were found to be eligible and entered randomization, 105 of whom being assigned to the SA3X group and 110 to the control group (Figure 1). The baseline characteristics in the two groups were similar (Table 1). Nearly 30% had diabetes mellitus and hypertension, and more than three-fourths were obese. Total testosterone levels averaged 230.34 ng/dL and 239.64 ng/dL at baseline in the SA3X and placebo groups, respectively (Table 1).

Efficacy results

SA3X therapy resulted in a significant increase ($P < 0.001$) in total serum testosterone levels at months 2, 3, and 6 compared with placebo. The

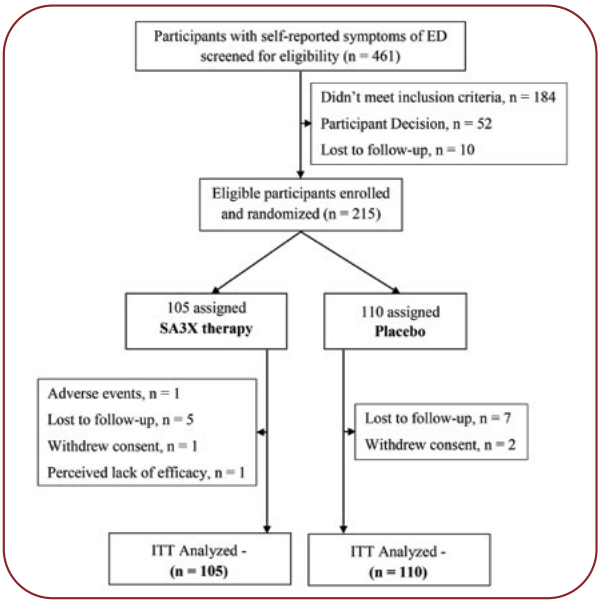

FIGURE 1. Participant flow diagram

TABLE 1. Participant characteristics (ITT population)

Characteristics	Total (N = 215)	SA3X therapy (N = 105)	Placebo (N = 110)	p-value
Age (years), mean ± SD	45.38 ± 3.15	45.86 ± 2.16	44.92 ± 3.72	0.13
BMI (kg/m²), mean ± SD	27.15 ± 4.58	27.95 ± 4.22	26.38 ± 5.88	0.21
Duration of penile erection (minutes), mean ± SD	1.79 ± 0.21	1.72 ± 0.15	1.84 ± 0.37	0.48
Baseline MSHQ score, mean ± SD	19.29 ± 3.99	18.65 ± 3.76	19.97 ± 4.19	0.12
Baseline IIEF score, mean ± SD	19.26 ± 3.14	19.12 ± 4.32	19.42 ± 2.19	0.44
Serum Testosterone (ng/dL), mean ± SD	236.78 ± 51.23	230.34 ± 57.12	239.64 ± 46.23	0.11
Comorbid conditions, n (%)				
• Diabetes mellitus	75 (34.88)	34 (32.38)	41 (37.27)	0.45
• Hypertension	64 (29.76)	29 (27.61)	35 (31.81)	0.50
• Hypercholesterolemia	49 (22.79)	21 (20.00)	28 (25.45)	0.34
• Cardiovascular diseases	18 (8.37)	8 (7.61)	10 (9.09)	0.69
• Thyroid disorders	7 (3.25)	3 (2.85)	4 (3.63)	0.74
Concomitant medications, n (%)				
• OHAs	61 (28.37)	28 (26.67)	33 (30.00)	0.58
• Anti – HTNs	49 (22.79)	21 (20.00)	28 (25.45)	0.34
• Statins	35 (16.27)	15 (14.28)	20 (18.18)	0.43
• Antidepressants	6 (2.79)	2 (1.91)	4 (3.63)	0.44
• PDE-5i (one month prior)	24 (11.16)	10 (9.52)	14 (12.72)	0.45

ITT=intention to treat; BMI=body mass index; MSHQ=Male Sexual Health Questionnaire; IIEF=International Index of Erectile Function; OHA=oral hypoglycemic agents; HTN=hypertensive; PDE-5i=phosphodiesterase-5 inhibitors

Characteristics	Visit (at the end of)	Treatment difference (SA3X therapy *vs.* placebo) estimate (mean ± SD)	p-value
Serum testosterone levels (ng/dL)	Month 1	3.01 ± 2.12	0.87
	Month 2	13.02 ± 3.11	0.02*
	Month 3	19.87 ± 4.21	<0.01*
	Month 6	18.32 ± 2.87	0.04*
Total MSHQ score	Month 1	14.53 ± 3.12	0.04*
	Month 2	15.76 ± 2.87	0.02*
	Month 3	17.05 ± 3.11	<0.01*
	Month 6	14.54 ± 2.77	0.03*
IIEF score	Month 1	14.85 ± 1.76	0.04*
	Month 2	16.05 ± 3.11	<0.01*
	Month 3	16.17 ± 2.98	<0.01*
	Month 6	15.21 ± 1.76	0.02*
Duration of penile erection (minutes)	Month 1	6.01 ± 1.43	0.01*
	Month 2	6.54 ± 2.01	0.01*
	Month 3	7.03 ± 2.83	<0.01*
	Month 6	7.01 ± 1.87	<0.01*

TABLE 2. Summary of MMRM analysis for change from baseline in serum testosterone levels (ITT population)

MMRM=Mixed Model Repeated Measures; ITT=intention to treat;
MSHQ: Male Sexual Health Questionnaire; IIEF=International Index of Erectile Function
*p<0.05

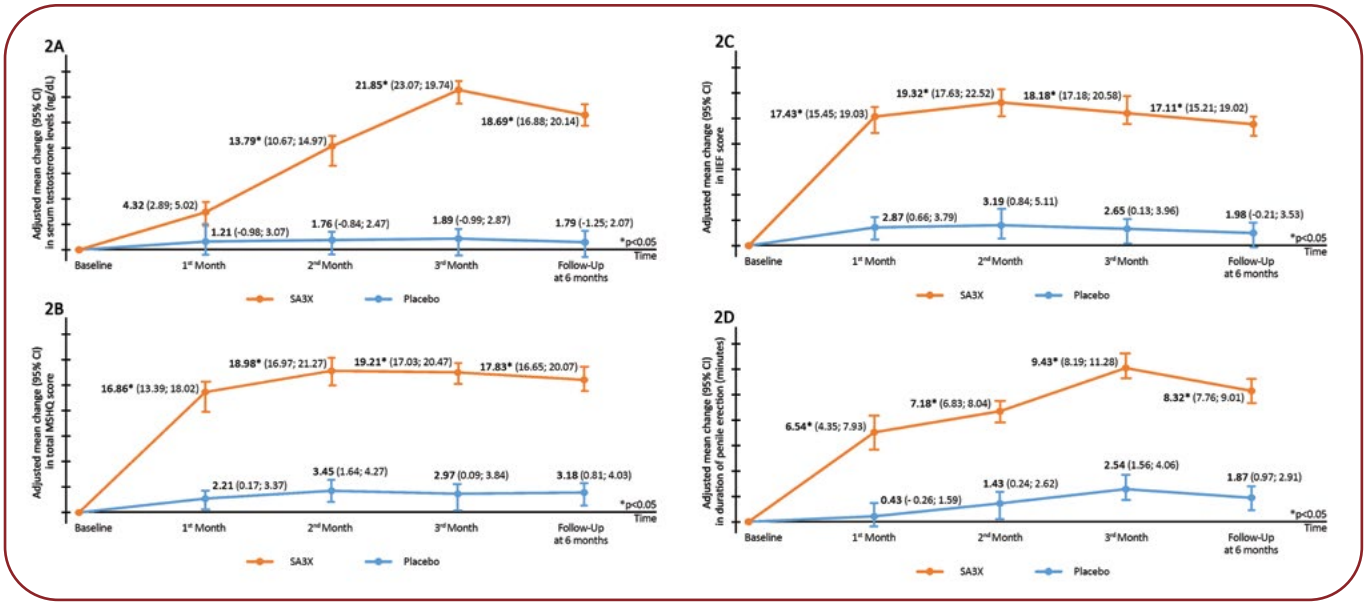

FIGURE 2. Adjusted mean (±SE) change in (2A) serum testosterone levels, (2B) MSHQ score, (2C) IIEF score, and (2D) duration of penile erection in the study population from baseline to month 3 of treatment, and follow-up at month 6 (ITT population)

adjusted mean change from baseline was 21.85 ng/dL in the SA3X therapy group *vs.* 1.89 ng/dL in the placebo group (Figure 2A). A significant difference in treatment was observed from month 2 (13.02 ± 3.11; p = 0.02) between the SA3X and placebo group, and the effects continued to month 3 (19.87 ± 4.21; p<0.01); the difference was also significant at the end of month 6 (18.32 ± 2.87; p = 0.04) even after discontinuation of intervention, as highlighted in Table 2.

Similar findings were also observed in the MSHQ score, IIEF score, and duration of penile erection. In all mentioned secondary outcomes, a significant difference was noted from month 1 of SA3X therapy, with a treatment difference of

Characteristics		Difference in change in serum testosterone levels at month 3† (mean ± SD)	p – value
Age (years)	< 50	18.76 ± 3.67	0.39
	≥ 50	21.51 ± 4.92	
BMI (kg/m²)	< 30	22.36 ± 1.32	0.02*
	≥ 30	16.65 ± 2.73	
Baseline serum testosterone (ng/dL)	< 250	19.54 ± 3.78	0.98
	≥ 250	20.32 ± 4.01	
Diabetes mellitus	Yes	16.32 ± 2.13	0.04*
	No	22.87 ± 3.64	
Hypertension	Yes	19.65 ± 2.76	0.52
	No	20.32 ± 3.12	
Hypercholesterolemia	Yes	15.95 ± 2.29	0.03*
	No	21.76 ± 3.11	
Cardiovascular diseases	Yes	18.87 ± 2.06	0.76
	No	20.12 ± 1.98	
Thyroid disorders	Yes	19.45 ± 2.87	0.29
	No	20.11 ± 1.65	
OHAs	Yes	16.59 ± 3.21	<0.01*
	No	21.65 ± 1.76	
Anti–HTN	Yes	19.65 ± 3.21	0.36
	No	20.43 ± 2.65	
Statins	Yes	14.98 ± 3.22	0.04*
	No	21.43 ± 2.19	
Antidepressants	Yes	18.79 ± 2.99	0.21
	No	19.96 ± 3.22	
PDE-5i (one month prior)	Yes	27.21 ± 2.76	<0.01*
	No	19.39 ± 2.98	

TABLE 3. Stratification of SA3X effect on serum testosterone levels

BMI=body mass index; OHA=oral hypoglycemic agents; HTN=hypertensive; PDE-5i=phosphodiesterase-5 inhibitors
*p<0.05
†Differences were calculated using the following equation: change in the testosterone group –change in the placebo group

	Total (N = 215)	SA3X therapy (N = 105)	Placebo (N = 110)	p-value
Fever	8 (3.72%)	3 (2.85%)	5 (4.54%)	0.51
Nausea/Vomiting	2 (0.93%)	1 (0.95%)	1 (0.91%)	0.97
Dysgeusia	9 (4.18%)	8 (7.61%)	1 (0.91%)	0.01*
Retrograde ejaculation	3 (1.39%)	1 (0.95%)	2 (1.81%)	0.58
Decreased semen volume	5 (2.32%)	3 (2.85%)	2 (1.81%)	0.61

TABLE 4. Summary of adverse events in the ITT population

ITT=intention to treat
*p<0.05

14.53 for MSHQ score, 14.85 for IIEF score, and 6.01 minutes for the duration of penile erection. (Table 2; Figure 2B – 2D).

Sensitivity analysis

The effect of SA3X on serum testosterone levels of participants with baseline testosterone levels less than 250 ng/dL or greater than equal to 250 ng/dL was similar. Moreover, the effect of SA3X on serum testosterone significantly differed by body mass index (<30 *vs.* ≥ 30 kg/m²), presence of diabetes, hypercholesterolemia, and consumption of medications such as oral hypoglycemics and statins. Intake of PDE5-i prior to one month of study significantly increased the effects of SA3X on testosterone levels (Table 3).

Adverse events

Except for dysgeusia, there was no difference in the frequency of adverse events between the

two groups. Dysgeusia increased significantly more in the SA3X group than the placebo one (P = 0.01) (Table 4). No SAEs were reported in this study. One patient developing dysgeusia withdrew from the study, and three patients from the SA3X group complained of decreased seminal volume.

DISCUSSION

In participants with ED who had low testosterone levels, addition of SA3X was associated with a more significant improvement in serum testosterone from month 2 compared with placebo. SA3X was superior to placebo in improving any domain of the sexual function, duration of penile erection, and frequency of total or satisfactory sexual encounters. Thus, this trial supports the supplementation of SA3X to improve testosterone levels and erectile response in participants with ED and low testosterone levels.

The concealed randomization, placebo control, blinding, and parallel-group design of the present were among its many positive trial design attributes. Randomization effectively generated two intervention groups that were similar in baseline characteristics. The sample size was determined after considering the statistical power and effect size. SA3X dose was optimized based on previous studies (21-23) and remained constant throughout the intervention. Mean serum testosterone levels at baseline evaluated using cutting-edge techniques in the current trial were significantly below the lower limits of normal determined in community-based samples and verified against results from epidemiologic studies (25, 29, 30). Rates of loss to follow-up were lower than those reported in other testosterone trials (31).

It is reassuring to find that trial data are internally consistent. The baseline characteristics of participants, including the prevalence of diabetes and hypertension, were typical of males with ED (32, 33). The administration of SA3X was associated with a marked and sustained increase in erectile function and other domains of the MSHQ and IIEF, similar to that reported in a previous trial (22). However, the presence of comorbid conditions and concomitant medications influenced the serum testosterone levels. Prior intake of PDE5-i seemed to increase the effects of SA3X. It was in accordance with a review by Spitzer *et al* (34), which established that administration of an optimized dose of PDE5-i to men with ED and low testosterone increased serum testosterone levels probably through a direct action on the testes. Even though age did not seem to affect the testosterone levels in the present study, evidence suggests otherwise (35, 36). This variation could have been possible due to the study population and the operational categorization in the study. Few studies evaluating the association between testosterone and comorbid conditions such as obesity and diabetes corroborate the findings of the current study (37-40).

The increase in testosterone along with improved erectile function in response to SA3X therapy reverberates with the studies suggesting that testosterone plays a vital role in penile erection, including enhancement of penile blood flow and venous occlusion, production of nitric oxide, and maintenance of penile smooth muscle mass (9-11, 41). Testosterone trials in males with hypogonadism have reported improvements in sexual activity scores (42, 43). Several explanations are possible. Testosterone levels increased by approximately 21.85 ng/dL after three-month supplementation of SA3X. The mechanisms by which SA3X administration may increase testosterone levels are poorly understood. It has been noted that *Spilanthes acmella* caused the steroidogenic acute regulatory protein and protein kinase G1 in male rats to become active (44, 45). SA3X may have increased testosterone levels to the higher limits of the dose-response relationship of testosterone for erectile function (15). The results are similar to studies where administration of an optimized dose of PDE5-i alone was associated with remarkable improvements in ED and other sexual function domains (46, 47).

The findings of the present trial should not be extrapolated to suggest that SA3X could replace PDE5-i or injectable testosterone as the mainstay of treatment for males with ED and low testosterone levels. Testosterone is an approved drug for treating ED in males and may have other beneficial effects on muscle strength, physical performance, body composition, cognition, and metabolism, which were not investigated in this trial. However, our results support the routine addition of SA3X as a supplement for improving erectile response in males with ED who have low testosterone levels.

The limitations of our study can be ascertained to the population belonging to a particular geographical area with a similar lifestyle and environmental exposure. Generalizing the findings to a broader population should be done with caution. Apart from the confounding factors evaluated in the study, other factors might be influencing serum testosterone levels that need to be assessed. The long-term effects of PDE5-i, if any, have not been considered in the current trial; however, the certainty of PDE5-i effects lasting beyond three months is questionable. The adverse effects evaluated here are limited to self-reported symptoms; biochemical assessment of specific haematological parameters like haematocrit, erythrocyte sedimentation rate, C-reactive protein, etc can provide a better estimate of how the drug interaction takes place.

CONCLUSION

Supplementation with SA3X for people with ED and low testosterone seems a plausible option as it significantly increases the serum testosterone levels along with erectile function. With dysgeusia being the only significant adverse effect reported, SA3X can be used for three months, and the biological effects persist for six months or more, as evident from this trial. The adverse effects assessed by us are purely symptomatic in nature and other biochemical parameters have to be evaluated. Furthermore, the interaction of SA3X and drugs such as PDE5-inhibitors, statins or alpha blockers, which are frequently used by older men with ED, should be assessed in future pharmacological studies. In order to claim external validity, further evidence needs to be generated through trials encompassing different population groups and geographical regions. ❑

Conflicts of interest: none declared.

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