Original research article

Urologia Journal

Urologia Journal
1–5

DOI: 10.1177/0391560318802160
journals.sagepub.com/home/urj
SAGE

Tribulus terrestris versus placebo in the treatment of erectile dysfunction and lower urinary tract symptoms in patients with late-onset hypogonadism: A placebo-controlled study

Sameh Fayek GamalEl Din[1], Mohamed Ahmed Abdel Salam[1], Mohamed Shokr Mohamed[1], Ahmed Ragab Ahmed[2], Ahmed Tarek Motawaa[1], Omar Ayman Saadeldin[1] and Ramzy Raafat Elnabarway[1]

Abstract

Aging is associated with a series of morphological and functional modifications that leads to reduced physiological efficiency and atrophy of various organs and systems. *Tribulus terrestris* induces its effect in fertility and sexual functions through the steroidal saponins, particularly the dominant saponins protodioscin. We aimed in this study to evaluate the efficacy and safety profiles of *Tribulus terrestris* in aging males with partial androgen deficiency who suffered from erectile dysfunction and lower urinary tract symptoms. A total of 70 randomized aging patients with erectile dysfunction and lower urinary tract symptoms were recruited from June 2017 to March 2018 from our andrology outpatient clinic. Thirty-five patients (group A) received *Tribulus terrestris* three times daily for 3 months and the other 35 patients (group B) received placebo. The mean of aspartate transaminase was elevated in group A after 3 months of receiving *Tribulus terrestris* (26.5 (before), 27.8 (after), respectively, $p = 0.03$). Moreover, there were significant elevations in the means of both total testosterone together with the score of the validated Arabic index of erectile function (5-item version of the International Index of Erectile Function) (2.2, 10.7 (before), 2.7, 16.1 (after), $p < 0.001$, $p < 0.001$, respectively). Finally, the mean of the total prostate-specific antigen was elevated in this group (1.4 (before), 1.7 (before), $p = 0.007$, respectively). Interestingly, there were no worsening of the lower urinary tract symptoms in group A as there was no change in the mean score of the international prostate symptom score, which was used to assess these symptoms before and after treatment (mean 14.4 (before), 14.6 (after), $p = 0.67$, respectively). In sum, this study replicates the findings of previous reports about the robust effect of this herbal medicine in elevating the testosterone level and improving the sexual function of patients who suffered from erectile dysfunction with partial androgen deficiency.

Keywords

Aging males with partial androgen deficiency, total testosterone, liver enzymes, validated Arabic version of erectile dysfunction (5-item version of the International Index of Erectile Function), International Prostate Symptom Score

Date received: 27 June 2018; accepted: 10 August 2018

Introduction

Aging is a slow physiological process. During this process, a series of morphological and functional modifications takes place within all organs, tissues, and cells that leads to reduced physiological efficiency and atrophy of various

[1]Department of Andrology & STDs, Cairo University, Cairo, Egypt
[2]Department of Andrology & STDs, Beni Suef University, Beni Suef, Egypt

Corresponding author:
Sameh Fayek GamalEl Din, Department of Andrology & STDs, Cairo University, Al-Saray Street, El Manial, Cairo 11956, Egypt.
Email: samehfayek@hotmail.com

organs and systems.[1,2] Reduced activities occur in both peripheral glandular secretions and hypothalamus and pituitary gland. Thus, aging process is associated with a fundamental change in the secretion of most hormones resulting in hypogonadism.[3] There are different terms for this form of hypogonadism such as late-onset hypogonadism (LOH), age-related hypogonadism, andropause, partial androgen deficiency in aging male (PADAM), androgen decline in the aging male (ADAM), or testosterone deficiency syndrome (TDS).[4] Older men are vulnerable to age-related hypogonadism that is defined as a clinical and biochemical disease characterized by serum testosterone level below the reference parameters of younger healthy men as well as symptoms of testosterone deficiency in the form of pronounced disturbances of the quality of life and harmful effects on multiple organ systems.[5] The incidence of biochemical hypogonadism in middle-aged men ranges from 2.1% to 12.8%,[6] while this incidence in men aged 40–79 years ranges from 2% to 6%.[6,7] The most characteristic features of LOH are erectile dysfunction, decreased sexual activity and loss of libido, decreased muscle strength, decreased vital energy, hot flashes, gynecomastia and decreased testicular volume, and low-energy consumption; in addition, non-specific features are decreased self-confidence, motivation, depression and irritability, memory and concentration impairment, sleep disorders or insomnia, and decreased psychomotor activity. Protodioscin is an Herbal Steroid Saponin extract derived mainly from *Tribulus terrestris* L. grown mainly in Bulgaria.[8]

This herb was used in traditional Chinese medicine.[9] Gauthaman and Ganesan[10] demonstrated that *Tribulus* induces its effect in fertility and sexual functions through the steroidal saponins, particularly the dominant saponins protodioscin (PTN). Moreover, Joseph[11] demonstrated that herbal remedies in the form of combined therapy of Bangshil and Fortege improved prostatic congestion as well as associated urinary symptoms namely burning micturition. Thus, we aimed in this study to evaluate the efficacy and safety profiles of *Tribulus terrestris* in aging males with partial androgen deficiency who suffered from erectile dysfunction and lower urinary tract symptoms.

Patients and methods

Study design and participants

A total of 70 randomized aging patients were recruited in this prospective study who suffered from partial androgen deficiency with erectile dysfunction. They were recruited from June 2017 to March 2018 from the andrology outpatient clinic, Cairo University. The patients were divided equally into two groups. One group received *Tribulus terrestris* three times daily for 3 months and the other group received placebo (starch granules) three times daily for 3 months. In this prospective trial, we used an extract of this herb that was standard to contain not more than 45% steroidal saponins (Trib Gold) that should be stored at room temperature according to the manufacturer. Each capsule contained 250 mg of *Tribulus terrestris* that was prescribed to the patients three times daily for 3 months; thus, 334.5 mg of PTN was provided to the patients in group A. At the beginning of the study, 5 mL blood was withdrawn from all the participants for baseline measurement of liver enzymes and total prostate-specific antigen (PSA-t), in addition to, testosterone (total).

Eventually, after 3 months, another 5 mL blood was withdrawn for a second measurement for the liver enzymes, PSA-t and total testosterone (TT). We assessed the participants at the beginning of the study and every month for 3 months using the validated Arabic version of the erectile function to determine the level of erection of the participants and International Prostatic Symptom Score (IPSS) to determine the presence and the severity of lower urinary tract symptoms (LUTS).[12,13] Genital examination was done to assess the consistency of the patients' testes and their volumes using Prader's orcidometer[14] and radiologically using scrotal ultrasound (SONOLINE G40, Diagnostic Ultrasound Systems, Manufactured by Siemens AG, Eriangen, Germany). Also, we examined the penis to detect any abnormality. Approval of the ethical committee was gained after getting a signed in writing consents from the participants that conforms to Helsinki declaration 1964.

Inclusion criteria of the participants

All the patients were in the age of 40–70 years old suffering from erectile dysfunction and partial androgen deficiency (TT $<$ 3.5 ng/mL).

Exclusion criteria of the participants

All patients who suffered from diabetes mellitus, hypertension, hepatic failure, chronic renal failure, or neurogenic illness such as hemiplegia were excluded from the study. Moreover, smoking, alcohol or drugs abuse, or any other drugs that may affect erectile function and patients with Peyronie's disease were also excluded from the study.

Statistical methods

Data were coded and entered using the statistical package SPSS (Statistical Package for the Social Sciences) version 25. Data were summarized using mean, standard deviation, median, minimum, and maximum in quantitative data. Comparisons between quantitative variables were done using the non-parametric Mann–Whitney test. For comparison of serial measurements within each patient, the non-parametric Wilcoxon signed-rank test was used.[15] A p value of less than 0.05 was considered as statistically significant.

Table 1. Age difference between group A who received *Tribulus terrestris* and group B who received placebo.

	Tribulus terrestris					Placebo					p value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
Age	55.69	9.35	55.00	40.00	72.00	58.38	9.71	59.50	40.00	70.00	0.433

SD: standard deviation.
The value of p was calculated used the Mann–Whitney test.

Table 2. Changes in liver enzymes, TT, validated Arabic international index of erectile function (IIEF-5), PSA-t, and IPSS before and after in group A who received *Tribulus terrestris*.

Tribulus terrestris	Before					After					p value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
ALT	24.09	4.64	23.00	18.00	38.00	24.66	3.88	24.00	19.00	31.00	0.940
AST	26.54	4.16	25.00	19.00	35.00	27.77	3.40	28.00	21.00	36.00	0.029
TT(T)	2.15	0.24	2.10	1.60	2.50	2.73	0.70	2.40	1.90	4.30	<0.001
IIEF-5	10.71	3.01	11.00	5.00	17.00	16.11	4.89	18.00	9.00	25.00	<0.001
PSA-t(T)	1.38	0.97	1.10	0.10	3.50	1.66	1.22	1.30	0.20	5.10	0.007
IPSS	14.43	9.70	15.00	0.00	32.00	14.60	9.28	15.00	0.00	33.00	0.674

SD: standard deviation; ALT: alanine transaminase; AST: aspartate transaminase; TT: total testosterone; IIEF-5: 5-item version of the International Index of Erectile Function; PSA-t: total prostate-specific antigen; IPSS: International Prostate Symptom Score.
The value of p was calculated using the Wilcoxon signed-rank test.

Results

A total of 70 randomized aging patients completed this prospective single-blind study. They were divided equally into two groups, group A who received *Tribulus terrestris* 250 mg daily for 3 months and group B who received placebo three times daily for 3 months. All the participants were in the age of 40–70 years and were equally distributed in group A and group B (mean = 55.7, 58.4 and standard deviation = ±9.4, 9.7, respectively) and this difference did not show any statistically significant result ($p = 0.4$) (Table 1). The mean of aspartate transaminase (AST) was elevated in group A after 3 months of receiving *Tribulus terrestris* (mean before and after were 26.5 and 27.8, respectively) and this demonstrated statistically significant result ($p = 0.03$) (Table 2). Moreover, there were significant elevations in the means of both TT together with the score of the validated Arabic index of erectile function (5-item version of the International Index of Erectile Function (IIEF-5)) (means of TT and IIEF-5 before and after were 2.2, 10.7 and 2.7, 16.1, respectively) and this revealed highly significant results ($p < 0.001$, $p < 0.001$, respectively) (Table 2).

Finally, the mean of the PSA-t was elevated in this group (mean before and after were 1.4 and 1.7, respectively) and this showed highly significant result ($p = 0.007$) (Table 2); 18, 32, and 20 participants suffered from severe (IPSS = 20–35), moderate (IPSS = 8–19), and mild (IPSS = 1–7) LUTS were recruited in this study and were divided equally in both groups. Interestingly, there were no worsening of the LUTS as there was no change in the mean score of the International Prostate Symptom Score (IPSS) which was used to assess these symptoms before and after treatment (mean before and after were 14.4 and 14.6, respectively) and this did not show any significant result ($p = 0.67$) (Table 2). On the other hand, there were insignificant changes in group B who received placebo three times daily for 3 months as regards liver enzymes, TT, validated Arabic international index of erectile function (IIEF-5), PSA-t, and IPSS (Table 3).

Discussion

The present randomized prospective trial demonstrated that *Tribulus terrestris* resulted in significant elevation in the mean TT level as well as the mean score of the validated Arabic version of the international index of erectile function in the participants of group A who received *Tribulus terrestris* three times daily for 3 months. Quite the reverse, there were insignificant changes in the mean TT as well as the mean score of the validated Arabic version of the international index of erectile function in the participants of group B who received placebo three times daily for 3 months. In the same context, McKay (2004) revealed that *Tribulus terrestris* has been used to treat the symptoms of low testosterone levels.[16]

Furthermore, Roaiah et al.[17] demonstrated high efficacy of this herbal medicine in improving the erectile function of aging patients with partial androgen deficiency and low libido. Moreover, several studies evaluated this herb in the

Table 3. Changes in liver enzymes, TT, validated Arabic international index of erectile function (IIEF-5), PSA-t, and IPSS before and after in group B who received placebo.

Placebo	Before					After					p value
	Mean	SD	Median	Minimum	Maximum	Mean	SD	Median	Minimum	Maximum	
ALT	19.88	6.45	20.50	9.00	32.00	19.50	5.40	18.00	13.00	30.00	0.831
AST	23.62	7.27	21.00	14.00	35.00	23.62	7.03	22.50	16.00	38.00	0.944
TT(T)	2.01	2.18	5.05	1.94	2.16	2.06	1.30	5.25	2.04	2.19	0.484
IIEF-5	10.75	2.55	10.50	7.00	14.00	10.62	2.72	10.00	7.00	14.00	0.564
PSA-t(T)	1.88	2.03	1.02	0.41	6.51	1.86	1.72	1.26	0.45	5.75	0.575
IPSS	9.00	8.59	6.00	2.00	28.00	9.62	8.37	7.50	2.00	28.00	0.096

SD: standard deviation; ALT: alanine transaminase; AST: aspartate transaminase; TT: total testosterone; IIEF-5: 5-item version of the International Index of Erectile Function; PSA-t: total prostate-specific antigen; IPSS: International Prostate Symptom Score.
The value of p was calculated using the Wilcoxon signed-rank test.

form a mixture together with other ingredients proved to efficacious in patients with erectile dysfunction.[18,19] Eventually, Kamenov et al.[20] showed that this herbal medicine was highly effective in improving the erectile function, intercourse satisfaction, sexual desire, orgasmic function, overall satisfaction as well as global efficacy questionnaire (GEQ) responses. In contrast, Santos et al.[21] showed that this herb was as effective as placebo in treating patients with erectile dysfunction. Recently, Abudayyak et al.[22] demonstrated that *Tribulus terrestris* should be used carefully because of its endocrine disrupting potential in the form of estrogenic activity that was noted from the water extracts of *Tribulus terrestris* at concentrations higher than 27 mg/mL (⩾2.6-fold) as well as antiandrogenic activity. However, the methanol and chloroform extracts of *Tribulus terrestris* demonstrated anti-estrogenic activity.[22] On the contrary, Kamenov et al.[20] did not report serious side effects from this medicine. Liver enzymes were measured at the beginning of the study and 3 months later on to evaluate the safety profile of this herbal medicine. Although, this herb was given for 3 months only; yet, there was minimal elevation in the mean of AST after 3 months of *Tribulus terrestris* supplementation to patients in group A. However, this difference was statistically significant (mean before and after were 26.5 and 28, respectively, $p=0.03$). Thus, this study alarms the necessity of regular follow-up of liver enzymes, especially when this herbal medicine is prescribed for long duration.

Besides, there was elevation in the mean of total PSA after 3 months of *Tribulus terrestris* supplementation to patients in group A and this difference was statistically highly significant (mean before and after were 1.4 and 1.7, respectively, $p=0.007$). This finding can be explained by the saturation model that was demonstrated by Morgentaler and Traish[23] that was based on the observation that the prostate exhibits high sensitivity to changes in androgens at low concentrations but little or no sensitivity to higher concentrations. However, there was no associated worsening of the LUTS in these patients as their mean IPSS score revealed insignificant change (mean before and after were 14.4 and 14.6, respectively, $p=0.67$).

The present trial did not demonstrate any improvement in the LUTS of the participants who received *Tribulus terrestris* three times daily for 3 months. In the same context, a critical review about the widespread use of herbal supplements in LUTS revealed the presence of scant scientific evidence to support their safety and efficacy.[24] Noteworthy, our study did not report any drop out and all the participants in both groups were compliant to *Tribulus terrestris* and placebo. Eventually, there are some limitations of this study that must be reported. First, the sample size was small and the patients were followed up for short duration. Second, cross over was not performed between both groups. Finally, kidney functions and free PSA were not evaluated.

Conclusion

In sum, this study replicates the findings of previous reports about the robust effect of this herbal medicine in elevating the testosterone level and improving the sexual function of patients who suffered from erectile dysfunction with partial androgen deficiency. There were minimal elevations in the mean of AST and PSA-t that happened after 3 months of supplementation to the patients in group A and were statistically significant. Thus, this study alarms the necessity of regular evaluation of liver enzymes and total PSA especially when this herbal medicine is prescribed for long duration.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) received no financial support for the research, authorship, and/or publication of this article.

ORCID iD

Sameh Fayek GamalEl Din https://orcid.org/0000-0003-1918-5132

References

1. Bromley DB. Przejawy biologiczne. Wprowadzenie. In: Bromley DB (ed.) *Psychologia Starzenia Się*. Warszawa: PWN, 1969, pp. 36–43.
2. Rolf C, Zitzmann M and Nieschlag E. Physiology of aging. In: Nieschlag E, Behre H and Nieschlag S (eds) *Male reproductive health and dysfunction*. 3rd ed., vol. 14. New York: Springer, 2010, pp. 239–240.
3. Dudek P, Kozakowski J and Zgliczyński W. Late-onset hypogonadism. *Menopause Rev* 2017; 16(2): 66–69.
4. Dohle GR, Arver S, Bettocchi C, et al. EAU Guidelines on male hypogonadism, 2015, www.uroweb.org/guidelines/onlineguidelines/
5. Wang C, Nieschlag E, Swerdloff F, et al. Investigation, treatment, and monitoring of late-onset hypogonadism in males: ISA, ISSAM, EAU, EAA, and ASA recommendations. *Eur Urol* 2009; 1: 121–130.
6. Hall SA, Esche GR, Araujo AB, et al. Correlates of low testosterone and symptomatic androgen deficiency in a population-based sample. *J Clin Endocrinol Metab* 2008; 93: 3870–3877.
7. Wu FC, Tajar A, Pye SR, et al. Hypothalamic-pituitary-testicular axis disruptions in older men are differentially linked to age and modifiable risk factors: the European Male Aging Study. *J Clin Endocrinol Metab* 2008; 93: 2737–2745.
8. Adimoelja A and Siauw AF. AB69. Phyto-androgenic androgens in men's health, sex and aging. *Transl Androl Urol* 2014; 3(Suppl. 1): AB69.
9. Selvam ABD. Inventory of vegetable crude drug samples housed in botanical survey of India, Howrah. *Pharmacogn Rev* 2008; 2(3): 61–94.
10. Gauthaman K and Ganesan AP. The hormonal effects of *Tribulus terrestris* and its role in the management of male erectile dysfunction – an evaluation using primates, rabbit and rat. *Phytomedicine* 2008; 15(1–2): 44–54.
11. Joseph MK. Bangshil and Fortege in prostatic congestion. *Curr Med Pract* 1980; 24: 311–315.
12. Shamloul R, Ghanem H and Abou-zeid A. Validity of the Arabic version of the sexual health inventory for men among Egyptians. *Int J Impot Res* 2004; 16: 452–455.
13. Bosch JL, Hop WC, Kirkels WJ, et al. The international prostate symptom score in a community-based sample of men between 55 and 74 years of age: prevalence and correlation of symptoms with age, prostate volume, flow rate and residual urine volume. *Br J Urol* 1995; 75(5): 622–630.
14. Prader A. Testicular size: assessment and clinical importance. *Triangle* 1966; 7: 240–243.
15. Chan YH. Biostatistics 102: quantitative data–parametric & non-parametric tests. *Singapore Med J* 2003; 44(8): 391–396.
16. McKay D. Nutrients and botanicals for erectile dysfunction: examining the evidence. *Altern Med Rev* 2004; 9(1): 4–16.
17. Roaiah MF, El Khayat YI, GamalEl Din SF, et al. Pilot study on the effect of botanical medicine (*Tribulus terrestris*) on serum testosterone level and erectile function in aging males with partial androgen deficiency (PADAM). *J Sex Marital Ther* 2015; 42(4): 297–301.
18. Kam SC, Do JM, Choi JH, et al. In vivo and in vitro animal investigation of the effect of a mixture of herbal extracts from *Tribulus terrestris* and *Cornus officinalis* on penile erection. *J Sex Med* 2012; 9(10): 2544–2551.
19. Sansalone S, Leonardi R, Antonini G, et al. Alga *Ecklonia bicyclis, Tribulus terrestris*, and glucosamine oligosaccharide improve erectile function, sexual quality of life, and ejaculation function in patients with moderate mild-moderate erectile dysfunction: a prospective, randomized, placebo-controlled, single-blinded study. *Biomed Res Int* 2014; 2014: 121396.
20. Kamenov Z, Fileva S, Kalinov K, et al. Evaluation of the efficacy and safety of *Tribulus terrestris* in male sexual dysfunction-a prospective, randomized, double-blind, placebo-controlled clinical trial. *Maturitas* 2017; 99: 20–26.
21. Santos CA, Reis LO, Destro-Saade R, et al. *Tribulus terrestris* versus placebo in the treatment of erectile dysfunction: a prospective, randomized, double blind study. *Actas Urol Esp* 2014; 38(4): 244–248.
22. Abudayyak M, Jannuzzi AT, Özhan G, et al. Investigation on the toxic potential of *Tribulus terrestris* in vitro. *Pharm Biol* 2015; 53(4): 469–476.
23. Morgentaler A and Traish AM. Shifting the paradigm of testosterone and prostate cancer: the saturation model and the limits of androgen-dependent growth. *Eur Urol* 2009; 55: 310–320.
24. Nabavizadeh R, Zangi M, Kim MM, et al. Herbal supplements for prostate enlargement: current state of the evidence. *Urology* 2017; 112: 145–150.