

A Pilot Study of a *T. terrestris*-*E. longifolia* Formulation to Enhance Endogenous Testosterone Production in Low Testosterone-Level Males

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Abstract

A small pilot study was performed examining the effect of a novel combination of *Tribulus terrestris* and *Eurycoma longifolia* (Tongkat) with micronutrients on endogenous testosterone production in men. A group of ten men was followed for four months, measuring total testosterone and estradiol. TSH was measured as a control of metabolic function. At the onset of the study, the average testosterone was 309 ng/dL; average estradiol was 12.3 ng/dL. At the end of four months of testing, the average testosterone had increased to 428 ng/dL; estradiol had increased to 19.8 ng/dL. Over the testing period, total endogenous testosterone production increased by 52.6% (+/- 5.6%)—without the exogenous introduction or application of any hormone or direct precursor.

Keywords: *Andropause; Aromatase; Estradiol; Libido; Testosterone*

Abbreviations

OTC: Over-the-Counter; SHBG: Sex Hormone-Binding Globulin; T: Time (Testing Time); TCM: Traditional Chinese Medicine; TSH: Thyroid-Stimulating Hormone

Introduction

Low testosterone levels in men: an “endocrinologic crisis”

The United States and other developed countries are undergoing an “endocrinologic crisis”. The last decade has seen increasing reports of lower testosterone values across nearly all cohorts of the American male population. One study reported an average of 501 ng/dL of testosterone in men aged 45–71, in 1987–1989. By 2002–2005, the average testosterone in men aged 57–80 had fallen to 391 ng/dL [1]. The average total testosterone value in American males has decreased dramatically since the mid-1900s [1-3], a trend that seems to correlate with the incidence and prevalence of diabetes mellitus and metabolic syndrome during the same period. The implications of these comparative findings are varied; however, the contributing factors in the decreasing testosterone values to the increasing rates of diabetes mellitus and metabolic syndrome have not gone unnoticed [4-7]. In men, multiple studies have supported that by increasing relatively low circulating levels of testosterone to approximately 500 ng/dl may help reduce diabetes mellitus and metabolic syndrome [8-12].

The depreciating testosterone levels appear in all age cohorts in the population suggesting that testosterone decline (in women as well as men) is not solely a consequence of aging but also of comorbidities and environmental factors. Thus, low testosterone levels cannot be considered a sequela of andropause alone, which is mostly age-based. This persistent and precipitous drop in testosterone levels has invoked a search for alternative therapies to boost endogenous testosterone production.

The limitations and risks of exogenous testosterone introduction and application

The direct exogenous introduction or application of testosterone in men in overt andropause and pre-andropause has been raised as a potential health risk; however, the probable risk remains undetermined. The results of a randomized control trial in older men showed that while men given exogenous hormone did exhibit significant improvement in libidos and sex lives, the subjective improvement was limited and reduced over time [13]. However, these findings were not well received, as punctuated by an accompanying editorial which criticized the study for choosing an older patient cohort that was seeking exogenous hormone augmentation, and denounced the study length as being inadequate to accurately assess longer-term health risks associated with exogenous hormone usage [14]. The use of exogenous testosterone supplementation is problematic as there is the possibility of testosterone aromatizing to estradiol and exacerbating andropausal symptoms, without additional pharmacologic therapies to block aromatase.

There are risks associated with testosterone's introduction into and application on the human body. The findings of a 2013 study linked exogenous testosterone usage with adverse cardiovascular events, in this retrospective, population-based controlled study of 928,745 men. A significantly increased incidence of venous thromboembolism was shown within six months of the onset of persistent exogenous testosterone therapy [15]. Moreover, a 2017 study revealed a connection between OTC testosterone-enhancing supplements with new-onset bilateral pulmonary embolism; with the author stating, "there is an inherent risk for vascular events, such as emboli, in testosterone supplement use" [16].

Inconclusive findings on individual herbal application in elevating low testosterone levels

Herbal extracts (in natural supplement form) have fared no better (than exogenous testosterone mentioned above) in the examination of their health benefits or risks. Earlier studies with the herbs fenugreek (*Trigonella foenum-graecum*) [16] and diindolylmethane (derived from cruciferous vegetables) [17] have been used in an attempt to alter androgen metabolism and human physiology. However, their mechanisms of action are unclear, possibly acting as an aromatase inhibitor or facilitating metabolism through estrone.

Later studies have shown that in men with hypogonadism and corresponding low testosterone values, there is a possible protective effect with testosterone augmentation in cardiovascular mortality [18]. However, a meta-analysis of hypogonadal men treated with testosterone revealed a slight risk of erythrocytosis (correlated mainly to levels of testosterone higher than the physiologic average for the age cohort); libido and sexual function saw marked improvement [19]. Most of these studies have been described as being short-term and biased [20]. Given the subjective nature of participant feedback, this bias is unlikely to be eliminated in any future, similar research. Most of these studies did not adequately control healthy androgen metabolism and production. Also, there is a logical flaw in assuming that nonproductive exogenous supplementation to supraphysiologic or high age-cohort controlled values will incur the same risks as demonstrated by a nonfeedback controlled application of testosterone.

The study of phytomedicinal approaches to boost the natural production of testosterone has been limited. The best anecdotal evidence for herbal approaches are from *Eurycoma longifolia* (e.g., *Tongkat ali* from TCM) and *Tribulus terrestris* (commonly used in Ayurvedic medicine). Most effects of these two herbs have been based on individual not combined application [21-31].

A proposed phytomedicine formula for promoting endogenous testosterone production in low testosterone-level males

The debate continues regarding the use and benefits of exogenous testosterone, herbal supplements, and phytomedicines to increase native testosterone production. Thus far, no significant studies have been performed or designed to examine a combination of phytomedicines (and other natural ingredients) to assess their combined effect on low testosterone levels in specific men. Hence, the following small pilot study was designed and performed, as described below.

Materials and Methods

Ten volunteer men aged 30–60 years, with self-described andropause symptoms of fatigue, anhedonia, decreased libido, and or weight gain, were pooled from a nutritional clinic patient-base in the Central Texas, USA. The patients were screened for a total testosterone level less than 500 ng/dL but higher than overt andropause at 120 ng/dL.

Participants were excluded if they were currently on OTC or prescription-support for the management of low testosterone. Also, the participants were instructed to avoid additional supplements or medications, and to continue with their typical diets or exercise habits during the study. All participants in the study had biologic children (not adopted), verifying reproductive ability.

The selected patients were not reimbursed for their participation but received free research materials; they paid for their labs (at cost). This lack of monetary incentive precipitated the need for a non-blinded, non-controlled study.

The *T. terrestris-E. longifolia* formulation used in the study was designed by James Meyer, PharmD, with collaboration from N.D. Victor Carsrud, MBBS, DC. Research materials were manufactured and provided gratis for the entire study by NuMedica, Inc., USA. No direct financial support or incentive was provided to any participant or researcher.

The *T. terrestris-E. longifolia* formulation was as follows, per 2-capsule dosage (with rationales for their selection):

- Zinc (as zinc bisglycinate chelate): 10 mg (to increase zinc-finger domain activity in testosterone metabolism).
- Longjack (*Eurycoma longifolia*; *Tongkat ali*): (Root extract) 300 mg (to enhance the endogenous production of testosterone).
- Ashwagandha (*Withania somnifera*): (Root extract, 4.5% withanolides) 250 mg (an adrenal adaptogen to reduce the conversion of testosterone to cortisol).
- *Tribulus terrestris*: (fruit extract, 60% saponins) 200 mg (to enhance the endogenous production of testosterone).
- Ginseng (*Panax ginseng*): (rhizome extract, 4% ginsenosides) 200 mg (an adrenal adaptogen to reduce the conversion of testosterone to cortisol).
- Nettle (*Urtica dioica*): (leaf extract, 4:1) 100 mg (to reduce the binding strength and efficacy of SHBG).
- Velvet bean (*Mucuna pruriens*): (seed extract, 99% L-Dopa) 100 mg (to increase dopamine concentration and, by association, testosterone).
- Grape (*Vitis vinifera*): (seed extract, 95% proanthocyanidins) 10 mg (to act as a preservative).

The participants were instructed to take two capsules twice per day for four months. Data points were taken at time zero, one month, two months, and four months. Total testosterone, Estradiol, and TSH were measured at each time point. TSH levels were included as a control value for significant variations in metabolic function during the study. Labs were collected and analyzed by LabCorp, USA.

Results

The average testosterone level at the beginning of the study was 309 ng/dL; the average estradiol level was 12.3 ng/dL. At the end of the study period and testing, the average testosterone had increased to 428 ng/dL; estradiol had increased to 19.8 ng/dL. These final values represented an averaged increase across four months of 52.6% (+/- 5.6%) in total.

The initial testosterone value average was 308.9 ng/dL (+/- 110.8), with a range of 159 - 427 ng/dL. The initial estradiol levels were 12.3 (+/- 5.9), with a range of 5 - 21.5 ng/dL. Subsequent months showed a steady increase in testosterone and estradiol levels, with no encroachment into abnormal or pathologic ranges. These results are summarized in Table 1.

Time Point	Avg Testosterone (ng/dL)	Avg Estradiol (ng/dL)	Avg TSH
T0	308.9 (+/- 110.8)	12.3 (+/- 5.9)	2.24 (+/- 1.6)
T1 (1 month)	389.9 (+/- 112.3)	18.0 (+/- 3.8)	2.59 (+/- 1.9)
T2 (2 months)	401 (+/- 137.0)	18.6 (+/- 4.39)	2.39 (+/- 1.8)
T3 (4 months)	427.6 (+/- 212)	19.9 (+/- 10.4)	2.42 (+/- 1.5)

Table 1: Total values from T0-T3 for testosterone and estradiol.

Note, a complication presented due to the wide variation in testosterone values that can elicit symptoms in presenting patients. The level changes from month to month (as a percentage from baseline for each patient) were recorded to standardize this variation and achieve a common baseline. The results of the percentage changes are summarized in Table 2.

Compared % change	% Testosterone change	% Estradiol Change	% TSH change
T0 to T1 (1 month)	34.7%	24%	17%
T0 to T2 (2 months)	35.8%	18.7%	9.8%
T0 to T3 (4 months)	52.6%	56.2%	4.3%

Table 2: The percentage of change from patient baseline T0 to subsequent time points.

Discussion

The foundation of this pilot study was to determine if it was possible to reproducibly increase endogenous steroidogenic production of testosterone using a phytomedicinal compound. The resultant increases in testosterone production (as determined by blood testosterone levels) from the onset of the study, through the first month, and continuing to the fourth and final month of the study suggest a cumulative and consistent upregulation of total testosterone production (Figures 1,2). However, based on the researchers’ clinical experience and the tapering of the slope in Figure 1, the production likely has an upper limit near the fourth month, just under 500 ng/dL within the study group. Men who began with higher values tended to stall in testosterone production just under this value, while those that began with lower values of testosterone continued to show level increases over time.

Further studies over a more extended period will be required to determine if there is an exact upper physiologic limit to stimulated production via this method, representing a physiologic ceiling. However, if an upper ceiling exists, it should limit and reduce the risk of excess estrogen production or erythrocytosis that is seen frequently in the misuse of exogenous steroids. Increases in SHBG concentration and binding affinity are contributing factors in this study that were not addressed.

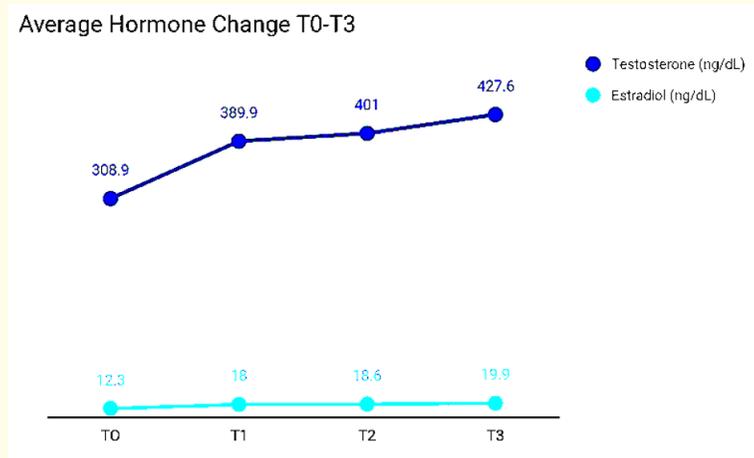


Figure 1: Total values T0-T3 for testosterone and estradiol.

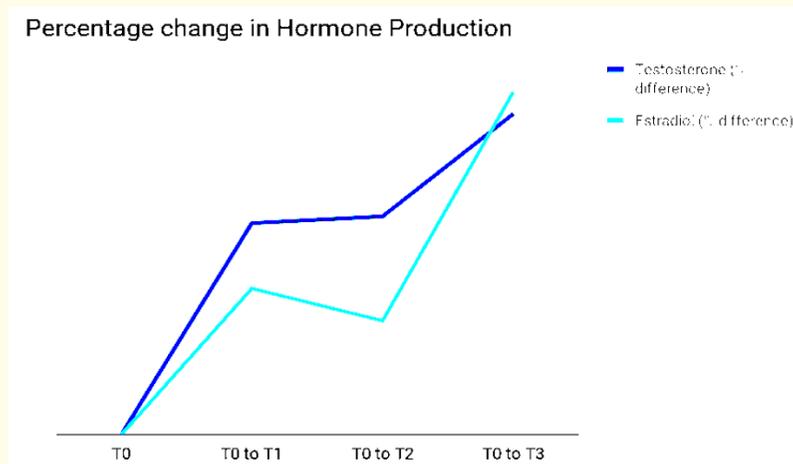


Figure 2: Percentage change from patient baseline T0.

Three of the participants were monitored for free testosterone, although this data was not collected from the initial time point; thus, the evaluation of this specific factor was unclear. One of the participant's free testosterone increased during T1 to T2 from 6.8 ng/dL to 12.3 ng/dL suggesting the formulation affected free testosterone percentage; the further investigation of this free testosterone observation was left for a future, more extensive study.

While there was a significant increase in estradiol production, it remained within normal ranges and values and mirrored the increased production of testosterone. The increases in testosterone and estradiol, within normal physiologic values, suggested upregulation in the integral endogenous production pathway, and a healthy balance between endogenous testosterone and estradiol concentrations

via normal aromatase function. It remains to be seen in more extensive studies whether the addition of an aromatase inhibitor might optimize the testosterone-estradiol balance further. (No participant began with abnormally high levels of estradiol; thus, it is assumed in these cases that aromatase function was normal.)

Based on the apparent upper limit in formula-enhanced testosterone production (as described previously), it may be inferred that there is a corresponding upper limit to induced estradiol production, likely remaining within physiologic limits as well. However, this observation would also need to be verified in subsequent, more extensive studies.

No significant differences across the study were observed in TSH concentration. It remains unlikely, therefore, that these increases in steroidogenesis seen in this study were secondary to an unexplained upregulation in cellular metabolism.

The uncertainties, risks, and costs involved in enhancing endogenous testosterone production via exogenous pharmaceutical agents are of concern not only for men seeking such augmentation but also for healthcare professionals providing such products or services. A convenient, affordable, and effective herbal formulation may have significant benefits for issues in men's health beyond libido and sexual function. Given testosterone's effects in reducing fasting blood sugar, the formulation tested in this study may prove to be a primary treatment or useful adjunct in reducing the risks for diabetes mellitus and metabolic syndrome as well as cardiovascular disease and specific forms of cancer.

Summary

Over a period of four months, a novel botanical combination of *Tribulus terrestris* and *Eurycoma longifolia* (with other natural ingredients) seemed to increase total testosterone production by 52%. The parallel changes in estradiol production suggested an upregulation in the steroidogenesis pathways and was not the result of the introduction of an exogenous precursor. The apparent upper limit to testosterone production—shown by a tapering of the slope of the production curve—suggested a physiologic ceiling, limiting a possible over-production of estradiol and risk of erythrocytosis. Further studies are needed to characterize these increases and investigate possible increases in the free testosterone percentage, as well as any longer-term adverse effects. This study suggests botanical stimulation of testosterone production may be a novel, convenient, and cost-effective application for men experiencing the sequelae of andropause, including diabetes, cardiovascular disease, osteoporosis, and various forms of cancer.

Conflict of Interest Statement

The authors declare that this paper was written in the absence of any commercial or financial relationship that could be construed as a potential conflict of interest.

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