Standardised water-soluble extract of *Eurycoma longifolia*, Tongkat ali, as testosterone booster for managing men with late-onset hypogonadism?

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Introduction

Natural therapy in the form of natural herbal supplementation has been the acceptable form of therapy for many people in most countries in the Orient as well as in Africa, South America and the Far East (Van Wyk *et al.*, 1997; Ernst, 2000; Gonzales *et al.*, 2002; Bratman & Girman, 2003; Valerio & Gonzales, 2005; Gonzales & Valerio, 2006; Tambi, 2009; Henkel *et al.*, unpublished). Such plants and/or herbal extracts are also used in managing wellness and general well-being related to ageing. However, in modern medicine very little is known about these alternative traditional approaches to combat diseases although 25% of prescriptions contain active ingredients extracted from plants (Castleman, 1995). In addition, very little is known about possible side effects of long-term treatments with these herbs as some of them also contain toxic substances. Therefore, an immense need exists to investigate the mode of molecular action of these herbs, their extracts and phytochemicals as conflicting results are published in literature reports.

Most of these plants like Mountain Ginseng (*Panax ginseng*) including a variety of their compounds were classified as adaptogens, meaning that these herbs or herbal compounds assist in combating stress and disease, improving physical strength without adverse effects. Compounds of *P. ginseng* have been found not to exert any effect to testosterone levels in the body (Perry & Metzger, 1980; Nocerino *et al.*, 2000; Bratman & Girman, 2003; MacKay, 2004). On the other hand, ‘Malaysian ginseng’...
(Eurycoma longifolia Jack; Simaroubaceae) or Tongkat ali, as it is known in Malaysia and indigenous to South-East Asia, is also regarded as adaptogen (Tambi, 2006).

Tongkat ali is an evergreen plant (Bhat & Karim, 2010), which is slowly growing up to 15–18 m in height on jungle slopes where they receive adequate shade and water (Bhat & Karim, 2010). The tree starts bearing fruits after 2–3 years, yet complete maturation takes up to 25 years. Its long, twisted roots are harvested, and aqueous concoctions are used by the local people to restore energy and vitality (Bhat & Karim, 2010) or for its aphrodisiac properties (Zanoli et al., 2009).

Particularly, the roots of E. longifolia contain a wide variety of chemical compounds including alkaloids, quassinoids, quassinoid diterpenoids, eurycomaoside, eurycolactone, laurycolactone or eurycomalactona (Morita et al., 1993; Ang et al., 2002; Bedir et al., 2003). Apart from these compounds, a bioactive peptide of 4.3 kDa with aphrodisiac properties has been identified (Ali & Saad, 1993; Sambandan et al., 2006; Asiah et al., 2007). The bioactive complex polypeptides from the Tongkat ali root extract, labelled as eurypeptides, exert and enhance their effects on the biosynthesis of various androgens (Ali & Saad, 1993). Unlike for other adaptogens, a wealth of animal studies is available pointing out aphrodisiac and testosterone enhancing effects of the root extract of Tongkat ali (Ang & Sim, 1998a,b). In contrast, properly conducted human studies are not available, except for a few short notices (Hamzah & Yusof, 2003; Tambi, 2006, 2009; Tambi & Imran, 2010).

As, according to traditional healers, Tongkat ali is supposed to be a suitable herbal supplement in treating male infertility and alleviating chronic low testosterone levels, this study aimed at investigating the usefulness of a treatment of hypogonadism men suffering from late-onset hypogonadism (LOH) with a patented standardised water-soluble extract of Tongkat ali (Sambandan et al., 2006; Phytes Bioteks, Biotropics Malaysia, Berhad, Malaysia) daily. After 1 month of treatment, follow-up examinations were conducted where AMS scores and the serum testosterone levels were recorded again. Of the 320 patients recruited for the study, only 76 subjects (Malay: n = 64, Indian: n = 9 and Chinese: n = 3) with LOH had regularly taken the Tongkat ali supplement and came for regular follow-up examinations. For this report, only data of men who completed a full course of Tongkat ali supplementation with a dose of 200-mg standardised water-soluble extract were taken into consideration.

Statistical analysis of the data was performed by using MedCalc (Ver. 11.3.3), MedCalc Software, Mariakerke, Belgium. Data were checked for normal distribution by means of the Kolmogorov–Smirnov test and expressed as mean ± standard deviation and Median ± range respectively. For analysis of categorical variables, patients were categorised regarding the results for AMS score and serum testosterone concentration: AMS: no complaints (AMS score 0) versus any complaint (AMS scores 1, 2 and 3); no/few complaints (AMS scores 0 and 1) versus mild/severe complaints (AMS scores 2 and 3). Similarly, the serum testosterone concentration was categorised into categories ‘normal’ (testosterone concentration 6–30.0 nm) versus ‘low’ (testosterone concentration <5.99 nm). For comparisons, appropriate statistical tests were applied and McNemar test was used, and P-values <0.05 were considered significant.

Results

Table 1 depicts the summary statistics for the parameters taken in this study. Data also revealed no difference between the different ethnic groups for any of the parameters taken.

As expected, significant correlations were observed between the patients’ age, the AMS scores and testosterone concentrations before and after the treatment with
Correlations between AMS score and the serum testosterone concentration are even highly significant ($P < 0.0001$).

Comparison of the parameters, AMS score and testosterone concentration before and after treatment revealed highly significant differences for both parameters (Figs 1 and 2). While the AMS score decreased from $38.05 \pm 9.25$ to $23.67 \pm 5.11$ after treatment, the testosterone concentration increased from $5.66 \pm 1.52$ to $8.31 \pm 2.47$ nm, which represents an average increase of 46.8%. These changes are highly significant ($P < 0.0001$). These improvements were seen in all individuals (results not shown).

After categorisation of the patients (Table 3) for the AMS scores and serum testosterone concentrations, the differences between paired proportions were calculated with the McNemar test. In fact, while before the treatment with the water-soluble Tongkat ali extract, only 10.5% ($n = 8$) of the patients did not show any complaints; this proportion increased to 71.7% ($n = 54$) after the treatment. The same improvement was observed for the serum testosterone concentration, which was normal in 35.5% ($n = 27$) before and in 90.8% ($n = 69$) of the patients after the treatment. Results of the McNemar tests show highly significant ($P < 0.0001$) improvements for both AMS score and serum testosterone concentration.

Table 1: Summary statistics of age, Ageing Males’ Symptoms (AMS) score and serum testosterone concentrations before and after treatment of patients with late-onset hypogonadism with 200 mg of the standardised water-soluble extract of Tongkat ali (Eurycoma longifolia) for 1 month

<table>
<thead>
<tr>
<th>Parameter</th>
<th>n</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>Minimum</th>
<th>Maximum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>76</td>
<td>51.00</td>
<td>10.06</td>
<td>52.00</td>
<td>28.00</td>
<td>70.00</td>
</tr>
<tr>
<td>AMS (before) (score)</td>
<td>76</td>
<td>38.05</td>
<td>9.25</td>
<td>38.00</td>
<td>23.00</td>
<td>58.00</td>
</tr>
<tr>
<td>AMS (after) (score)</td>
<td>76</td>
<td>23.67</td>
<td>5.11</td>
<td>24.00</td>
<td>17.00</td>
<td>38.00</td>
</tr>
<tr>
<td>Testosterone (before) (nm)</td>
<td>76</td>
<td>5.66</td>
<td>1.51</td>
<td>5.60</td>
<td>2.54</td>
<td>9.80</td>
</tr>
<tr>
<td>Testosterone (after) (nm)</td>
<td>76</td>
<td>8.31</td>
<td>2.47</td>
<td>7.60</td>
<td>4.20</td>
<td>18.00</td>
</tr>
</tbody>
</table>

Table 2: Spearman rank correlations between age, Ageing Males’ Symptoms (AMS) scores and serum testosterone (nm) in 76 late-onset hypogonadism (LOH) patients before and after intervention with 200-mg standardised water-soluble extract of Tongkat ali (Eurycoma longifolia) for 1 month. Significant positive and negative correlations between parameters are obvious, particularly between the AMS scores and testosterone concentrations before and after treatment of the LOH patients with 200-mg standardised water-soluble extract of Tongkat ali (E. longifolia) for 1 month

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AMS (before) (score)</th>
<th>AMS (after) (score)</th>
<th>Testosterone (before) (nm)</th>
<th>Testosterone (after) (nm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>Correlation coefficient 0.271</td>
<td>0.260</td>
<td>$-0.317$</td>
<td>$-0.211$</td>
</tr>
<tr>
<td></td>
<td>Significance level ($P$) 0.0178</td>
<td>0.0296</td>
<td>0.0053</td>
<td>0.0670</td>
</tr>
<tr>
<td></td>
<td>n                     76</td>
<td>76</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>AMS (before score)</td>
<td>Correlation coefficient 0.710</td>
<td>$-0.904$</td>
<td>$-0.463$</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Significance level ($P$) &lt;0.0001</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>n                     76</td>
<td>76</td>
<td>76</td>
<td>76</td>
</tr>
<tr>
<td>AMS (after score)</td>
<td>Correlation coefficient $-0.717$</td>
<td>$-0.740$</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Significance level ($P$) &lt;0.0001</td>
<td>&lt;0.0001</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>n                     76</td>
<td>76</td>
<td>76</td>
<td>76</td>
</tr>
</tbody>
</table>

Fig. 1 Serum testosterone concentration in 76 late-onset hypogonadism patients before and after treatment with 200-mg standardised water-soluble extract of Tongkat ali (Eurycoma longifolia) for 1 month. A highly significant increase in the testosterone concentration was calculated by means of the Wilcoxon test ($P < 0.0001$).
Discussion

Eurycoma longifolia Jack (Malaysian ginseng), locally known as Tongkat Ali, is traditionally used to treat a variety of illnesses including fever, aches, hypertension, tuberculosis, vermifuge and sexual insufficiency and erectile dysfunction. With regard to its said aphrodisiac properties, several animal studies using the rat as model revealed increased sexual motivation and performance (Ang & Sim, 1997, 1998a; Ang and Sim, 1998b; Ang & Ngai, 2001; Ang & Lee, 2002; Ang et al., 2000, 2003) including increased serum testosterone concentrations in treated rats (Zanoli et al., 2009). On the contrary, Lin et al. (2001) reported that a crude ethanol extract of Tongkat ali roots decreased the basal testosterone release, but increased the hCG-induced synthesis of the male sex hormone in rat Leydig cells.

Considering that the herbal extract of Tongkat Ali is used by traditional healers to treat sexual dysfunctions including erectile dysfunction and scientific studies in humans are lacking (Low & Tan, 2007), this is the first study that aimed at investigating the extract’s effects on patients suffering from LOH and confirming the testosterone stimulating properties of the standardised water-soluble extract of Tongkat ali in the human. Increased testosterone levels also alleviated AMS according to the AMS rating scale (Heinemann et al., 1999).

The molecular mechanism, by which root extract from E. longifolia is acting, is most probably through the bioactive complex eurypeptides that exert and enhance their effect on the biosynthesis of various androgens (Ali & Saad, 1993). The eurypeptide works by activating the CYP17 (17α-hydroxylase/17, 20 lyase) enzyme to enhance the metabolism of pregnenolone and 17-OH-pregnenolone to yield more dehydroepiandrosterone (DHEA) as well as the metabolism of progesterone and 17-OH-progesterone to 4-androstenedione and to testosterone (Ali & Saad, 1993).

In conclusion, the standardised water-soluble extract of Tongkat ali proved to be a suitable herbal supplement in overcoming symptoms of LOH and managing hypogonadism. Similarly, men with other causes of hypogonadism may also benefit by taking the herbal extract as an adjunct to their testosterone replacement therapy to enhance their DHEA. Moreover, a treatment like this may be a reasonable therapy for numerous patients, particularly in Third World or emerging countries as such herbal extracts are often cheaper than Western pharmaceutical medicines. In Malaysia, for instance, the supplement is available in most leading pharmacies and popular as a male health supplement. Yet,

Table 3  Distribution of Ageing Males’ Symptoms (AMS) categories and the serum testosterone concentration in 76 late-onset hypogonadism patients before and after intervention with 200-mg standardised water-soluble extract of Tongkat ali (Eurycoma longifolia) for 1 month. Calculation of McNemar tests for the differences between paired proportions (AMS: no complaints versus any complaint and no/few complaints versus mild/severe complaints; testosterone concentration: normal versus low) before and after the treatment with Tongkat ali resulted in highly significant (P < 0.0001) improvements for both the AMS score and serum testosterone concentration

<table>
<thead>
<tr>
<th>Category</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Category</th>
<th>Testosterone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AMS score n (%)</td>
<td>Testosterone concentration n (%)</td>
<td>AMS score n (%)</td>
<td>Testosterone concentration n (%)</td>
</tr>
<tr>
<td>0</td>
<td>No complaints</td>
<td>Normal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>Few complaints</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Mild complaints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>Severe complaints</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Low = testosterone concentration <5.99 nm; normal = testosterone concentration is between 6.00 and 30.0 nm.

McNemar tests:
a,b No complaint (AMS: 0) versus any complaint (AMS: 1, 2, 3): P < 0.0001.

c,d No/few complaints (AMS: 0, 1) versus mild/severe complaints (AMS: 2, 3): P < 0.0001.

e Normal testosterone concentration versus low testosterone concentration: P < 0.0001.
randomised placebo-controlled studies investigating the positive effects of Tongkat ali on ageing male well-being including its effects on the prostate are missing in the literature thus far and are currently underway.

References


