First International Journal of Andrology
ANDROLOGIA

ORIGINAL ARTICLE

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

M. I. B. M. Tambi[1,2], M. K. Imran[2] & R. R. Henkel[3]

1 Wellmen Clinic, Damai Service Hospital, Kuala Lumpur, Malaysia;
2 Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia, Kbg Kerian, Kelantan, Malaysia;
3 Department of Medical Bioscience, University of the Western Cape, Bellville, South Africa

Keywords
Adaptogen—*Eurycoma longifolia*—Hypogonadism—late-onset hypogonadism—testosterone—Tongkat ali

Correspondence
Prof. Mohd Ismail Bin Mohd Tambi, Wellmen Clinic, Damai Service Hospital, Kuala Lumpur 52100, Malaysia.
Tel.: +603 4043 4900 (Ext 791);
Fax: +603 4043 5399;
E-mail: dr_tambi@yahoo.com

Accepted: December 7, 2010

doi: 10.1111/j.1439-0272.2011.01168.x

Summary

In most countries, millions of people are relying on herbal medicines as remedy for numerous ailments. In South-East Asia, *Eurycoma longifolia* Jack, also known as 'Malaysian ginseng' or Tongkat ali, is used to combat stress and disease and to improve physical strength. Moreover, the compounds of the roots of this plant are reported to have aphrodisiac and testosterone enhancing effects in the rat. Considering that human studies are not available, 76 of 320 patients suffering from late-onset hypogonadism (LOH) were given 200 mg of a standardised water-soluble extract of Tongkat ali for 1 month. The Ageing Males' Symptoms (AMS) according to the standardised rating scale and the serum testosterone concentration were taken. Results show that treatment of LOH patients with this Tongkat ali extract significantly ($P < 0.0001$) improved the AMS score as well as the serum testosterone concentration. While before treatment only 10.5% of the patients did not show any complaint according to the AMS scale and 35.5% had normal testosterone levels, after the completed treatment 71.7% and 90.8% of the patients showed normal values, respectively. Thus, Tongkat ali extract appears to be useful as a supplement in overcoming the symptoms of LOH and for the management of hypogonadism.

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 hypogonadic men suffering from late-onset hypogonadism (LOH) with a patented standardised water-soluble extract of Tongkat ali in a retrospective analysis.

Materials and methods

This study had received ethical clearance from the Ethics Committee of the Ministry of Health of Malaysia.

In the period from 2005 until 2009, a total of 850 male subjects of different ethnicity attended the Wellmen Clinic at Damai Service Hospital, Kuala Lumpur, Malaysia, for hypogonadism. Of these, 320 patients gave informed consent and opted for the treatment of symptoms of hypogonadism and LOH (Jockenhövel, 2004; Wang *et al.*, 2008) with Tongkat ali. Patients were identified using the Ageing Males' Symptoms (AMS) Rating Scale (Heinemann *et al.*, 1999) as well as serum testosterone levels (below 6 nmol testosterone per litre; normal range: 6–30 nM). The AMS score was categorised as follows: score '0' from 17 to 26: 'no complaints'; score '1' from 27 to 36: 'few complaints'; score '2' from 37 to 49: 'mild complaints'; and score '3' at or above 50: 'severe complaints'. Similarly, the serum testosterone concentration was categorised into category '0' (normal: testosterone concentration 6–30.0 nM); '1' (low: testosterone concentration <5.99 nM). Serum testosterone levels were determined using a competitive immunoassay using direct chemiluminescent technology (ADVIA Centaur Testosterone assay; Bayer, Newbury, UK) according to the manufacturer's instructions.

Patients were treated with 200 mg (two capsules with 100 mg) of the 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

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

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

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

		AMS (before) (score)	AMS (after) (score)	Testosterone (before) (nm)	Testosterone (after) (nm)
Age (years)	Correlation coefficient	0.271	0.260	−0.317	−0.211
	Significance level (*P*)	0.0178	0.0236	0.0053	0.0670
	n	76	76	76	76
AMS (before score)	Correlation coefficient		0.710	−0.904	−0.463
	Significance level (*P*)		<0.0001	<0.0001	<0.0001
	n		76	76	76
AMS (after score)	Correlation coefficient			−0.717	−0.740
	Significance level (*P*)			<0.0001	<0.0001
	n			76	76

Tongkat ali (Table 2). 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 ± 9.25 to 23.67 ± 5.11 after treatment, the testosterone concentration increased from 5.66 ± 1.52 to 8.31 ± 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.

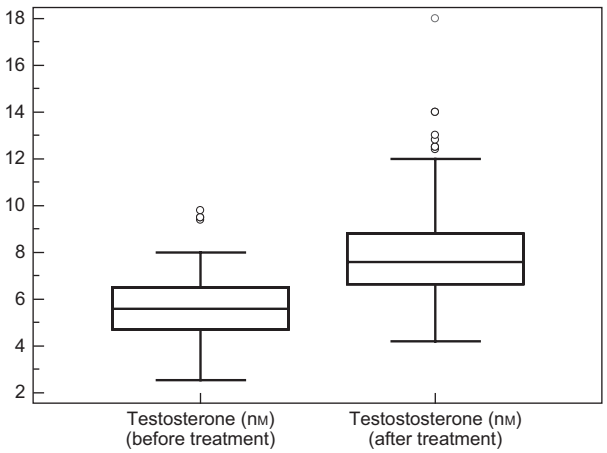

Fig. 1 Serum testosterone concentration in 76 late-onset hypogonadism patients before and after treatment with 200-mg standardised water-soluble extract of Tongkat ali (*Eurycoma longifolia*) for 1 month. A highly significant increase in the testosterone concentration was calculated by means of the Wilcoxon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

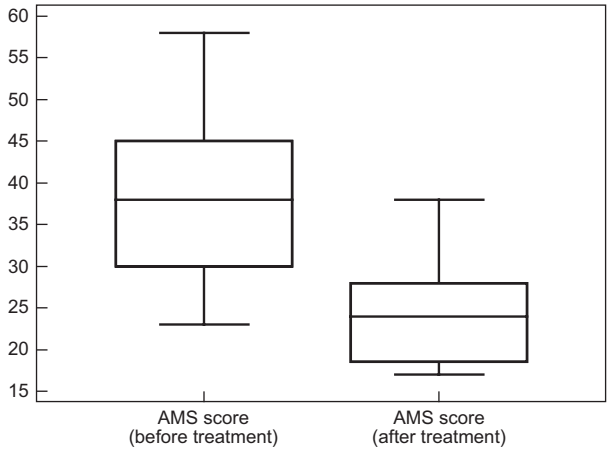

Fig. 2 Ageing Males' Symptoms (AMS) rating score in 76 late-onset hypogonadism patients before and after treatment with 200-mg standardised water-soluble extract of Tongkat ali (*Eurycoma longifolia*) for 1 month. A highly significant decrease in the AMS score was calculated by means of the Wilcoxon 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 (17 α-hyroxylase/17, 20 lyase) enzyme to enhance the metabolism of pregnenolone and 17-OH-pregnenolone to yield more dehyroepiandrosterone (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

Before treatment		After treatment		Category		
AMS score *n* (%)	Testosterone concentration *n* (%)	AMS score *n* (%)	Testosterone concentration *n* (%)	AMS		Testosterone
8 (10.5)	27 (35.5)	54 (71.1)	69 (90.8)	0	No complaints[a,c]	Normal[e]
25 (32.9)	49 (64.5)	21 (27.6)	7 (9.2)	1	Few complaints[b,c]	Low[f]
33 (43.4)	0 (0.0)	1 (1.3)	0 (0.0)	2	Mild complaints[b,d]	
10 (13.2)		0 (0.0)		3	Severe complaints[b,d]	

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,f]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

Ali JM, Saad JM (1993) Biochemical effect of *Eurycoma Longifolia* Jack on the sexual behavior, fertility, sex hormone and glycolysis [Dissertation]. Department of Biochemistry, University of Malaya.

Ang HH, Lee KL (2002) Effect of *Eurycoma longifolia* Jack on orientation activities in middle-aged male rats. *Fundam Clin Pharmacol* 16:479–483.

Ang HH, Ngai TH (2001) Aphrodisiac evaluation in non-copulator male rats after chronic administration of *Eurycoma longifolia* Jack. *Fundam Clin Pharmacol* 15:265268.

Ang HH, Sim MK (1997) *Eurycoma longifolia* Jack enhances libido in sexually experienced male rats. *Exp Anim* 46:287–290.

Ang HH, Sim MK (1998a) *Eurycoma longifolia* increases sexual motivation in sexually naive male rats. *Arch Pharm Res* 21:779–781.

Ang HH, Sim MK (1998b) *Eurycoma longifolia* Jack and orientation activities in sexually experienced male rats. *Biol Pharm Bull* 21:153–155.

Ang HH, Cheang HS, Yusof AP (2000) Effects of *Eurycoma longifolia* Jack (Tongkat Ali) on the initiation of sexual performance of inexperienced castrated male rats. *Exp Anim* 49:35–38.

Ang HH, Hitotsuyanagi Y, Fukuya H, Takeya K (2002) Quassinoids from *Eurycoma longifolia*. *Phytochemistry* 59:833–837.

Ang HH, Ngai TH, Tan TH (2003) Effects of *Eurycoma longifolia* Jack on sexual qualities in middle aged male rats. *Phytomedicine* 10:590–593.

Asiah O, Nurhanan MY, Ilham MA (2007) Determination of bioactive peptide (4.3 kDa) as an aphrodisiac marker in six Malaysia plants. *J Tropical Forest Sci* 19:61–63.

Bedir E, Abou-Gazar H, Ngwendson JN, Khan IA (2003) Eurycomaoiside: a new quassinoid-type glycoside from the root of *Eurycoma longifolia*. *Chem Pharm Bull (Tokyo)* 51:1301–1303.

Bhat R, Karim AA (2010) Tongkat ali (*Eurycoma longifolia* Jack): a review on its ethnobotany and pharmacological importance. *Fitoterapia* 10:1–11.

Bratman S, Girman A (2003) Mosby's Handbook of Herbs and Supplements and their Therapeutic Uses. Mosby Inc., St. Louis, MO, pp 976–978.

Castleman M (1995) Healing Herbs. Bantam Books, New York, pp 1–5.

Ernst E (2000) The role of complementary and alternative medicine. *BMJ* 321:1133–1135.

Gonzales GF, Valerio LG Jr (2006) Medicinal plants from Peru: a review of plants as potential agents against cancer. *Anticancer Agents Med Chem* 6:429–444.

Gonzales GF, Cordova A, Vega K, Chung A, Villena A, Gonez C, Castillo S (2002) Effect of *Lepidium meyenii* (MACA) on sexual desire and its absent relationship with serum testosterone levels in adult healthy men. *Andrologia* 34:367–372.

Hamzah S, Yusof A (2003) The ergogenic effects of Tongkat Ali (*Eurycoma longifolia*). *Br J Sports Med* 37:465–466.

Heinemann LAJ, Zimmermann T, Vermeulen A, Thiel C (1999) A new 'Aging Male's Symptoms' (AMS) rating scale. *The Aging Male* 2:105–114.

Jockenhövel F (2004) Male Hypogonadism. Uni-Med Verlag, Bremen, Germany, pp 118–134.

Lin LC, Peng CY, Wang HS, Lee KWW (2001) Reinvestigation of the chemical constituents of *Eurycoma longifolia*. *Chin Pharm J* 53:97–106.

Low WY, Tan HM (2007) Asian traditional medicine for erectile dysfunction. *JMHG* 4:245–250.

MacKay D (2004) Nutrients and botanicals for erectile dysfunction: examining the evidence. *Altern Med Rev* 9:4–16.

Morita H, Kishi E, Takeya K, Itokawa H, Iitaka Y (1993) Squalene derivatives from *Eurycoma longifolia*. *Phytochemistry* 4:765–771.

Nocerino E, Amato M, Izzo AA (2000) The aphrodisiac and adaptogenic properties of ginseng. *Fitoterapia* 71:S1–S5.

Perry LM, Metzger J (1980) Medicinal Plants of Southeast Asia: Attributed Properties and Uses. MIT Press, Cambridge.

Sambandan TG, Rha C, Aminudim N, Saad JM, Kadir AA (2006) Bioactive fraction of *Eurycoma longifolia*. Patent number: WO0217946; Other reference numbers: JP2004521075, US2004087493, EP1313491, DK1313491, DE60125955.

Tambi MI (2006) *Eurycoma Longifolia* Jack: a potent adaptogen in the form of water-soluble extract with the effect of maintaining men's health. *Asian J Androl* 8(Suppl. 1):49–50.

Tambi MI (2009) Nutrients and botanicals for optimizing men's health. Examining the evidence for *Eurycoma longifolia* Jack, the Malaysian Ginseng in men. *Asian J Androl* 11(Suppl. 5):37–38.

Tambi MI, Imran MK (2010) *Eurycoma longifolia* Jack in managing idiopathic male infertility. *Asian J Androl* 12:376–380.

Valerio LG Jr, Gonzales GF (2005) Toxicological aspects of the South American herbs cat's claw (*Uncaria tomentosa*) and Maca (*Lepidium meyenii*): a critical synopsis. *Toxicol Rev* 24:11–35.

Van Wyk B, Van Oudtshoorn B, Gericke N (1997) Medicinal Plants of South Africa. Briza Publishers, Pretoria, South Africa.

Wang C, Nieschlag E, Swerdloff R, Behre HM, Hellstrom WJ, Gooren LJ, Kaufman JM, Legros JJ, Lunenfeld B, Morales A, Morley JE, Schulman C, Thompson IM, Weidner W, Wu FCW (2008) Investigation, treatment and monitoring of late-onset hypogonadism in males. ISA, ISSAM, EAU, EAA and ASA recommendations. *Eur J Endocrinol* 159:507–514.

Zanoli P, Zavatti M, Montanari C, Baraldi M (2009) Influence of *Eurycoma longifolia* on the copulatory activity of sexually sluggish and impotent male rats. *J Ethnopharmacol* 126:308–313.