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An Evidence-Based Systematic Review of Tongkat Ali (*Eurycoma longifolia*) by the Natural Standard Research Collaboration

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ABSTRACT. An evidence-based systematic review of tongkat ali (*Eurycoma longifolia*) by the Natural Standard Research Collaboration consolidates the safety and efficacy data available in the scientific literature using a validated, reproducible grading rationale. This article includes written and statistical analysis of clinical trials, plus a compilation of expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

KEYWORDS. adverse effects, dosing, Eurycoma longifolia, evidence-based, interactions, pharmacodynamics, pharmacokinetics, pharmacology, systematic review, tongkat ali.

SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE

Search Strategy

To prepare this Natural Standard review, electronic searches were conducted in several databases (including AMED, CANCERLIT, CINAHL, CISCOM, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT) from inception to August 2011. Search terms included the common name(s), scientific name(s), and all listed synonyms. Hand searches were conducted of 20 additional journals (not indexed in common databases), and of bibliographies from 50 selected secondary references. No restrictions were placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) were consulted for access to additional references or ongoing research.

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Selection Criteria

All literature was collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, human data). Standardized inclusion/exclusion criteria were utilized for selection.

Data Analysis

Data extraction and analysis were performed by healthcare professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertained to each review section (defining inclusion/exclusion criteria and analytic techniques, including validated measures of study quality). Data were verified by a second reviewer.

Review Process

A blinded review was conducted by multidisciplinary research-clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, CAM research, and clinical practice. In cases of editorial disagreement, a three-member panel of the Editorial Board addressed conflicts, and consulted experts when applicable. Authors of studies were contacted when clarification was required.

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Synonyms/Common Names/Related Substances

- 1,2-Seco-1-nor-6(5 > 10)abeo-picrasan-2,5-olide skeleton quassinoids, 1beta, 12alpha,15beta-triacetyleurycomanone, 1-hydroxy-9-methoxycanthin-6-one, 3-methylcanthin-5,6-dione, 4,5,7,8,17-penta-hydr-oxy-14,18-dimethyl-6-methyl-ene-3,10-dioxapenta-cyclo-[9.8.0.0.0.0]nona-dec-14-ene-9,16-dione methanol solvate dehydrate, 5,6-dehydroeurycomalactone, 5alpha,14beta,15beta-trihydroxyklaineanone, 5-hydroxymethyl-9-methoxycanthin-6-one, 6alpha-hydroxyeurycomalactone, 6-dehydroxylongilactone, 7alpha-hydroxyeurycom alactone, 9,10-dimethoxycanthin-6-one, 9-hydroxycanthin-6-one, 9-hydroxy canthin-6-one n-oxide, 9-methooxycanthin-6-one, 9-methoxycanthin-6-one,9-methoxycanthin-6-one n-oxide, 10-hydroxy-9-methoxycanthin-6-one, 10-hydroxycanthin-6-one, 11-dehydroklaineanone, 12-epi-11-dehydroklaineanone, 13–21-dihydroeurycomanone, 13alpha,21-dihydroeurycomanone, 13alpha(21)-epoxyeurycomanone, 13beta,18-dihydroeurycomanol, 13beta,21-dihydroxy-eurycomanol, 13-beta-21-dihydroxyeurycomanone, 14,15beta-dihydroxyklai neanone, 14-deacetyleurylene, 15beta-acetyl-14-hydroxyklaineanone, 23,24,25-trihydroxytirucall-7-en-3,6-dione, aervin, Ali's cane, Ali's walking stick, amino acids, anthraquinone, anthraquinone glucosides, babi kurus (Javanese), bedara merah (Malay), bedara putih (Malay), beta-7-methoxycarboline-1-propionic acid, beta-carboline alkaloids, beta-carboline-1-propionic acid, bidara

laut (Indonesian), biphenylneolignans (2-hydroxy-3,2′,6′-trimethoxy-4′-(2,3-epoxy-1-hydroxypropyl)-5-(3-hydroxy-1-propenyl)-biphenyl and 2-hydroxy-3,2′-dimethoxy-4′-(2,3-epoxy-1-hydroxypropyl)-5-(3-hydroxy-1-propenyl)biphenyl), bitter charm, bitter medicine, C18 quassinoids, C19 skeleton quassinoids, C20-skeleton quassinoids, campesterol, canthin-6-one alkaloids (4,9-dimethoxycanthin-6-one, 10-hydroxy-11-methoxycanthin-6-one, 9,10-dimethoxycanthin-6-one, 11-hydroxy-10-methoxycanthin-6-one, 5,9-dimethoxycanthin-6-one, and 9-methoxy-3-methylcanthin-5,6-dione), cay ba binh (Vietnamese), dihydroniloticin, eurycolactone B, eurycolactone D, eurycolactone E, eurycolactone F, *Eurycoma apiculata*, *Eurycoma harmandiana*, *Eurycoma longifolia* Jack, Eurycoma Madu, eurycomalactone, eurycomalide A, eurycomalide B, eurycomanol, eurycomanol-2-O-beta-D-glucoside, eurycomanone, eurycomaoside, eurylactone A, eurylactone B, Force Pill Tongkat Ali, Great Pill Tongkat Ali Plus, laurycolactone A, laurycolactone B, lempedu pahit (Malay), longilactone, Malaysian ginseng, M-Tongkat Ali, muntah bumi (Malay), n-pentyl beta-carboline-1-propionate, oxasqualenoid, pasakbumin B, pasak bumi (Malay), payong ali (Malay), penawar bias (Malay), penawar pahit (Malay), petala bumi (Malay), plalaipeag, saponins, Simaroubaceae (family), sitosterol, squalene-type triterpenes (eurylene, 14-deacetyl eurylene, and longilene peroxide), stigmasterol, Sukarno Tongkat Ali, Super Pill Tongkat Ali, Super Pill Tongkat Ali Plus, TA-a, TA-b, Tender Pill Tongkat Ali, teurilene, tho nan (Laotian), tirucallane-type triterpenes (niloticin, dihydroniloticin, piscidinol A, bourjotinolone A, 3-episapelin A, melianone, and hispidone), tongka ali tea, tongkat ali, tongkat ali hitam, and tongkat baginda.

- *Combination products*. Etana (*Panax quinquefolius*, *Eurycoma longifolia*, *Epimedium grandiflorum*, *Centella asiatica*, flower pollen extracts).

CLINICAL BOTTOM LINE/EFFECTIVENESS

Brief Background

- *Eurycoma longifolia* is a tall, slender, shrubby tree which grows in sandy soil. It belongs to the Simaroubaceae family. It commonly grows wild in Southeast Asian countries such as Malaysia, Indonesia, Thailand, and Myanmar (Abd Rahman, Niiyama, & Azizi, 2002; Baharuddin, Adenan, & Mashhor, 1990; Chua et al., 1995; Chua et al., 2005) and is planted in Malaysia for its medicinal value in order to conserve the wild plants (Ang et al., 2001; Kulip, 2009; Mohd, 1998; Mohd, Amran, & Mohd, 2001). *Eurycoma longifolia* is traditionally known as "tongkat ali".
- *Eurycoma longifolia* is traditionally used in Malaysia as an aphrodisiac and to cure sexual dysfunction, as well as for its antipyretic, antimalarial, antibiotic, and antidiabetic properties. Although tongkat ali is traditionally used mainly in males, it is thought to have aphrodisiac properties in females as well. It is commonly thought that *Eurycoma longifolia* stimulates testosterone levels, resulting in increased sexual desire and ability, as well as increased athletic ability and muscle strength. However, very few studies are available investigating the effect of this

herb on testosterone levels in humans, as most studies have been conducted in animal models.
- At this time, clinical data in support of *Eurycoma longifolia* are lacking for any indication, and further research is required before conclusions can be drawn.

Scientific Evidence

Athletic endurance	C
Enhanced muscle mass/strength	C
Male fertility	C

Natural Standard Evidence-Based Validated Grading Rationale™

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and historic/folkloric precedent are not included in this assessment, and are reflected in a separate section of each review ("Expert Opinion and Historic/Folkloric Precedent").
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

Level of Evidence Grade	Criteria
A (strong scientific evidence)	Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.
B (good scientific evidence)	Statistically significant evidence of benefit from 1-2 properly randomized trials, OR evidence of benefit from >1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/nonrandomized trials AND with supporting evidence in basic science, animal studies, or theory.
C (unclear or conflicting scientific evidence)	Evidence of benefit from >1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from >1 cohort/case-control/nonrandomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory.
D (fair negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/nonrandomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.
F (strong negative scientific evidence)	Statistically significant negative evidence (i.e., lack of evidence of benefit) from >1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*
Lack of evidence†	Unable to evaluate efficacy due to lack of adequate available human data.

Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al., in which a score below 4 is considered to indicate lesser quality methodologically (Jadad et al., 1996).
†Listed separately in the "Historical or Theoretical Uses That Lack Sufficient Evidence" section.

Historical or Theoretical Uses That Lack Sufficient Evidence

- Adaptogen, aging, antibacterial, anxiety, aphrodisiac (Adaikan, 2004; Hussein, Rusli, & Kiong, 2007), appetite stimulant (Vittachi, 1994), cancer, constipation, diabetes (Remli & Chan, 2003), exercise recovery, fever, increased energy, increased strength, insecticide, leukemia, malaria, osteoporosis, sexual dysfunction (Adimoelja, 2000; Chye, 2006), stress, and syphilis.

Expert Opinion and Historic/Folkloric Precedent

- There are over 200 tongkat ali preparations on the market in Malaysia (Ang, 2004). The supply and demand of *Eurycoma longifolia* in Malaysia has been discussed (Muhammed & Haron, 2001). Approximately 21,000 kg of *Eurycoma longifolia* are harvested by collectors per year, with a demand of approximately 54,189 kg per year.
- In Malaysia, tongkat ali is used by patients with diabetes (Remli & Chan, 2003), and most men with erectile dysfunction questioned in a survey had used traditional medicines such as tongkat ali (Ab Rahman, Al-Sadat, & Yun Low, 2011). *Eurycoma longifolia* is traditionally used medicinally by the Jah Hut people in Malaysia (Lin, 2005). A community-based survey of people from peninsular Malaysia was conducted, but the results pertaining to *Eurycoma longifolia* are unclear (Al-Adhroey, Nor, Al-Mekhlafi, & Mahmud, 2010). In Malaysia, public knowledge about herbal beverages was investigated by questionnaire, but the results pertaining to *Eurycoma longifolia* are not clear at this time (Hassali et al., 2009).
- The genetic diversity of *Eurycoma longifolia* is thinning due to widespread harvesting; thus, single nucleotide polymorphisms have been used to study the remaining diversity (Osman et al., 2003), and microsatellite markers have been studied as tools for DNA profiling and genetic diversity studies (Tnah et al., 2011).
- Some scientists are interested in the in vitro production of the *Eurycoma longifolia* plantlets or plant tissues for sustainable production of active ingredients (Aziz, Akeng, & Kandasamy, 2000; Danial et al., 2005; Hasnida et al., 2001; Hussein et al., 2005; Hussein, Rusli, & Kiong, 2006; Maziah, Rosli, & Sreeramanan, 2010; Siregar & Keng, 2002; Sobri, Marziah, & Azizol, 2002). Ling et al. developed a protocol to optimize protoplast isolation from callus of *Eurycoma longifolia* (Ling et al., 2010).
- Various general reviews including *Eurycoma longifolia* have been published (Ahmad, 1996).
- *Eurycoma longifolia* is not listed on the U.S. Food and Drug Administration (FDA) Generally Recognized as Safe (GRAS) list.

Brief Safety Summary

- Possibly safe: When used at commonly suggested levels, based on history of use. There is little information available on adverse effects associated with *Eurycoma longifolia*.
- Possibly unsafe: When used in patients using hypoglycemic agents (Husen, Pihie, & Nallappan, 2004). When used in people with weakened immune systems

(according to secondary sources). When used in individuals using propranolol (Salman et al., 2010).

- Likely unsafe: When used in men with breast cancer or prostate cancer, diabetes mellitus, heart disease, kidney disease, liver disease, or sleep apnea, according to secondary sources. When used in children or pregnant or lactating women, due to a lack of sufficient safety data. When used in patients with known allergy or hypersensitivity to *Eurycoma longifolia*, its constituents, or members of the Simaroubaceae family.

DOSING/TOXICOLOGY

General

- Listed doses are based on those most commonly used in available trials, on historical practice, or on manufacturer recommendations. However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active components of a product are, standardization may not be possible, and the clinical effects of different brands may not be comparable.

Standardization

- There is no well-known standardization for *Eurycoma longifolia*.
- Doustjalali et al. published a report discussing a gel-based proteomic kit to screen the quality of water-soluble root extracts of *Eurycoma longifolia* (Doustjalali, Marzalina, & Datiakma, 2005). A convenient thin-layer chromatography (TLC) analysis was discussed for the detection of *Eurycoma longifolia* Jack in a food supplement (Carratu, Boniglia, Ciarrocchi, Gargiulo, & Sanzini, 2010). It was determined that there was no *Eurycoma longifolia* Jack in a product with this herb listed on the ingredient label.
- Teh, Murugaiyah, & Chan (2011) developed a validated liquid chromatography-mass spectrometric method for the simultaneous analysis of five quassinoid markers in order to standardize manufactured batches of *Eurycoma longifolia* Jack extract. The quassinoids included eurycomanone, 13alpha(21)-epoxyeurycomanone, eurycomanol, eurycomanol-2-O-beta-D-glucopyranoside, and 13,21-dihydroeurycomanone. The batches contained 5.65–9.95% of eurycomanone, 5.21–19.75% of eurycomanol, 7.59–19.95% of eurycomanol-2-O-beta-D-glucopyranoside, 0.78–3.90% of 13alpha(21)-epoxyeurycomanone, and 0.47–1.76% of 13,21-dihydroeurycomanone.
- Athimulam et al. discussed the modeling and optimization of *Eurycoma longifolia* water extract production (Athimulam et al., 2006). The optimization used SuperPro Designer®, a commercial batch process simulator. The authors achieved a product yield of 3.00%, with an annual production of 1,137.72 kg of extract. The modeling and optimization of *Eurycoma longifolia* extraction utilizing a recirculating flow extractor was also discussed (Mohd Ridzuan, Noor, Rain, Zhari, & Zakiah, 2005). A higher final yield than batch extraction was produced (7.70% (w/w) for the recirculating flow extractor and 6.67% (w/w) for the batch extraction).

Dosing

Adult (age ≥ 18)

Oral.

- *Endurance*. *Eurycoma longifolia* (two 75 mg capsules) daily for seven days and 1 hr prior to exercise had a lack of effect on endurance running capacity (Muhamad et al., 2010).
- *Enhanced muscle mass*. 100 mg of an *Eurycoma longifolia* extract daily for five weeks along with an exercise training program resulted in increased muscle mass and strength vs. the exercise program alone (Hamzah & Yusof, 2003). According to secondary sources, 300 mg of premium *Eurycoma* or 900 mg of lesser-grade material has been used daily for an unknown duration. According to secondary sources, alternate use of *Eurycoma* during prohormone off-cycles to restore natural testosterone harmony, and for year-round use, a five-days-on/two-days-off regimen for up to eight weeks, followed by a two-week break have been used. According to secondary sources, 400–800 mg of *Eurycoma longifolia* Jack has been taken as one or two doses (one dose about one hour or less before workout) for an unknown duration.
- *Male fertility*. Two 100 mg capsules orally of a proprietary standardized water-soluble extract of *Eurycoma longifolia* Jack root (U.S. Patent: US7,132,117B2 from Phytes Bioteks, Biotropics Malaysia, Berhad, Malaysia), twice daily after eating, for up to three cycles (nine months), improved parameters of semen analysis (Tambi & Imran, 2010).

Children (age < 18)

- Insufficient available evidence.

Toxicology

- Based on secondary sources, a water soluble extract of *Eurycoma longifolia* (LJ100) lacked toxicity in humans.
- Full acute and subacute toxicity studies showed no toxic effects of Etana, a herbal combination containing *Panax quinquefolius*, *Eurycoma longifolia*, *Epimedium grandiflorum*, *Centella asiatica*, and flower pollen extracts, in rats (Qinna, Taha, Matalka, & Badwan, 2009).
- An extract and some fractions of *Eurycoma longifolia* had cytotoxic effects against two mammalian cell lines (Vero and Hs27) commonly used for in vitro toxoplasmicidal evaluation (Nowroji et al., 2012). Cytotoxic effects of *Eurycoma longifolia* extracts have been shown in the human cell lines Hep2 and HFL1 (Mohd-Fuat, Kofi, & Allan, 2007).
- Acute toxicity studies in mice found that the n-butanol fraction of *Eurycoma longifolia* was the most toxic, mainly due to eurycomanone (Chan et al., 2012). In brine shrimp, 13,21-dihydroeurycomanone, eurycomanol, longilactone, 14,15beta-dihydroxyklaineanone, and eurycomanol-2-O-beta-glucopyranoside were 2.8, 33, 44, 88.9, and >100 times less toxic, respectively. Other toxic constituents included a C20-type quassinoid, an alpha,beta-unsaturated ketone in

ring A, an exomethylene function at C-13, and an oxymethylene bridge connecting C-8 and C-11 of ring C.

- Ang et al. reported on *Eurycoma longifolia* with respect to mercury and lead and quality requirements (Ang, 2004; Ang & Lee, 2006; Ang, Lee, & Matsumoto, 2003). The authors indicated that up to 36% of products tested contained measurable levels of mercury and lead and that some failed quality requirements.

ADVERSE EFFECTS/PRECAUTIONS/CONTRAINDICATIONS

Allergy

- Avoid with known allergy or hypersensitivity to *Eurycoma longifolia*, its constituents, or members of the Simaroubaceae family.

Adverse Effects

- *General*. There is little information available on the adverse effects associated with *Eurycoma longifolia*. According to secondary sources, reported side effects include insomnia, anxiety, and restlessness.
- *Musculoskeletal*. According to secondary sources, reported side effects include restlessness.
- *Neurologic/CNS*. According to secondary sources, reported side effects include insomnia.
- *Psychiatric*. According to secondary sources, reported side effects include anxiety.

Precautions/Warnings/Contraindications

- Use cautiously in patients using hypoglycemic agents, based on studies in animals suggesting that *Eurycoma longifolia* reduced blood glucose in hyperglycemic animals (Husen et al., 2004) and unpublished studies in humans suggesting the possibility for increased blood glucose.
- Use cautiously in people with weakened immune systems, as some evidence suggests that it may further weaken immune function, according to secondary sources.
- Use cautiously in individuals using propranolol as, in healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).
- Avoid in men with breast cancer or prostate cancer, diabetes mellitus, heart disease, kidney disease, liver disease, or sleep apnea, according to secondary sources.
- Avoid in children and pregnant and lactating women, due to a lack of sufficient safety data.
- Avoid in patients with known allergy or hypersensitivity to *Eurycoma longifolia*, its constituents, or members of the Simaroubaceae family.

Pregnancy and Lactation

- Not suggested due to lack of sufficient data.
- Information on *Eurycoma longifolia*'s effects on lactation is lacking in the National Institute of Health's Lactation and Toxicology Database (LactMed).

INTERACTIONS

Eurycoma longifolia/Drug Interactions

- *Antiadrenergic*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).
- *Antianxiety agents*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010). In mice, extract fractions of *Eurycoma longifolia* had anxiolytic effects, resulting in decreased fighting and more exploration in an open field test (measures willingness to explore) (Ang & Cheang, 1999a; 1999b). The extract increased the number of squares crossed in the test and increased mobility. In the elevated-maze test, the extract increased the number of entries and time spent in open arms and decreased the number of entries and time spent in closed arms (test of anxiety based on rodents' dislike of open arms).
- *Antibiotics*. Alcoholic, acetone, and aqueous extracts of *Eurycoma longifolia* had antibacterial effects against various Gram-negative and Gram-positive bacteria (Farouk & Benafri, 2007; Reddy, Nurdijati, & Salleh, 2010).
- *Antidiabetics*. In animal research, *Eurycoma longifolia* reduced blood glucose in hyperglycemic animals (Husen et al., 2004).
- *Antihypertensives*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).
- *Antimalarials*. In animal research, parasitemia suppression of *Plasmodium yoelii*-infected mice was shown (Mohd Ridzuan et al., 2007). Ethanol and methanol-ethanol extracts of roots and constituents of *Eurycoma longifolia* had antiplasmodial effects against *Plasmodium falciparum* in culture (Ang, Chan, & Mak, 1995; Ang, Chan, & Mak, 1995a; 1995b; Hout et al., 2006; Jiwajinda et al., 2002; Sriwilaijaroen et al., 2010). In animal research, a combination of *Eurycoma longifolia* extract and artemisinin improved parasitemia suppression of *Plasmodium yoelii*-infected mice vs. artemisinin alone (Mohd Ridzuan et al., 2007).
- *Antineoplastics*. In vitro, quassinoid constituents and extracts of *Eurycoma longifolia* were cytotoxic against cancer cell lines (Itokawa et al., 1993; Jiwajinda et al., 2002; Kuo et al., 2003; Miyake, Li, Tezuka, Awale, & Kadota, 2010; Morita et al., 1993; Nurhanan, Azimahtol, & Azizol, 2002; Nurhanan et al., 2005).
- *Antiobesity agents*. In humans, *Eurycoma longifolia* increased fat free mass, reduced body fat, and increased muscle strength and size (Hamzah & Yusof, 2003).
- *Beta-blockers (beta-adrenergic antagonists)*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).
- *Cardiovascular agents*: In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).
- *Cytochrome P450-modifying agents*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010). Conversely, in vitro, the effects of *Eurycoma longifolia* were considered negligible by the authors against cytochrome P450 enzymes (Hanapi et al., 2010).

- *Drugs used for osteoporosis*. In an aged orchidectomized rat model, *Eurycoma longifolia* had antiosteoporotic (maintaining bone calcium levels) effects (Shuid et al., 2011).
- *Ergogenic agents*. The ergogenic effects of *Eurycoma longifolia* were discussed in a review (Muhamad et al., 2009).
- *Fertility agents*. In humans, sperm motility significantly increased with use of *Eurycoma longifolia* (Tambi & Imran, 2010). In animal studies, *Eurycoma longifolia* increased copulatory behavior in noncopulator, middle-aged, or sexually sluggish and impotent male rats (Ang & Cheang, 1999a; 1999b; Ang & Cheang, 2002; Ang & Lee, 2002; Ang & Ngai, 2001; Ang & Sim, 1998; Zanoli, Zavatti, Montanari, & Baraldi, 2009); increased episodes of penile reflexes in male rats (Ang, Ikeda, & Gan, 2001); increased aphrodisiac and sexual motivation enhancement effects in sexually naïve male mice (Ang et al., 1997; Ang, Lee, & Kiyoshi, 2003; Ang & Sim, 1998) and rats (Ang & Sim, 1998); and decreased sexual hesitation in middle-aged rats (Ang, Ngai, & Tan, 2003). In animal research, *Eurycoma longifolia* fractions increased sexual orientation activities in middle-aged male rats (Ang & Lee, 2002) and sexual orientation activities and mounting frequency in sexually experienced male rats (Ang & Sim, 1997; Ang & Sim, 1998). In male rats, *Eurycoma longifolia* improved sexual performance (Ang et al., 1997). Improved sperm parameters (sperm count, motility, and viability) (Chan, Low, Teh, & Das, 2009; Mahanem, Abu Hassan, & Lukman, 2004; Wahab, Mokhtar, Halim, & Das, 2010) and testosterone (Chan et al., 2009) have also been shown in animal models.
- *Heart rate-regulating agents*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).
- *Hormonal agents*. Eurycomanone, a constituent of *Eurycoma longifolia*, had antiestrogenic effects against the 17alpha-ethynylestradiol (EE)-induced uterotrophy of immature rats (Teh et al., 2011). In animal research, *Eurycoma longifolia* increased testosterone levels (Chan et al., 2009).
- *Immunosuppressants*. According to secondary sources, *Eurycoma longifolia* should not be used by people taking immunosuppressant drugs.
- *Propranolol*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).
- *Sympatholytics*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).

Eurycoma Longifolia/Herb/Supplement Interactions

- *Antiadrenergic*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).
- *Antiarrhythmics*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).
- *Antibacterials*. Alcoholic, acetone, and aqueous extracts of *Eurycoma longifolia* had antibacterial effects against various Gram-negative and Gram-positive bacteria (Farouk & Benafri, 2007; Reddy et al., 2010).

- *Antimalarials*. In animal research, parasitemia suppression of *Plasmodium yoelii*-infected mice was shown (Mohd Ridzuan et al., 2007). Ethanol and methanol-ethanol extracts of roots and constituents of *Eurycoma longifolia* had antiplasmodial effects against *Plasmodium falciparum* in culture (Ang et al., 1995; Ang et al., 1995; Hout et al., 2006; Jiwajinda et al., 2002; Sriwilaijaroen et al., 2010).
- *Antineoplastics*. In vitro, quassinoid constituents and extracts of *Eurycoma longifolia* were cytotoxic against cancer cell lines (Itokawa et al., 1993; Jiwajinda et al., 2002; Kuo et al., 2003; Miyake et al., 2010; Morita et al., 1993; Nurhanan et al., 2002; Nurhanan et al., 2005).
- *Antiobesity agents*. In humans, *Eurycoma longifolia* increased fat free mass, reduced body fat, and increased muscle strength and size (Hamzah & Yusof, 2003).
- *Cardiovascular agents*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).
- *Cytochrome P450-modifying agents*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010). Conversely, in vitro, the effects of *Eurycoma longifolia* were considered negligible by the authors against cytochrome P450 enzymes (Hanapi et al., 2010).
- *Ergogenic agents*. The ergogenic effects of *Eurycoma longifolia* were discussed in a review (Muhamad et al., 2009).
- *Fertility agents*. In humans, sperm motility significantly increased with use of *Eurycoma longifolia* (Tambi & Imran, 2010). In animal studies, *Eurycoma longifolia* increased copulatory behavior in noncopulator, middle-aged, or sexually sluggish and impotent male rats (Ang & Cheang, 1999a; 1999b; Ang & Cheang, 2002; Ang & Lee, 2002; Ang & Ngai, 2001; Ang & Sim, 1998; Zanoli et al., 2009); increased episodes of penile reflexes in male rats (Ang et al., 2001); increased aphrodisiac and sexual motivation enhancement effects in sexually naïve male mice (Ang & Sim, 1998; Ang et al., 1997; Ang et al., 2003) and rats (Ang & Sim, 1998); and decreased sexual hesitation in middle-aged rats (Ang et al., 2003). In animal research, *Eurycoma longifolia* fractions increased sexual orientation activities in middle-aged male rats (Ang & Lee, 2002) and sexual orientation activities and mounting frequency in sexually experienced male rats (Ang & Sim, 1997; Ang & Sim, 1998). In male rats, *Eurycoma longifolia* improved sexual performance (Ang et al., 1997). Improved sperm parameters (sperm count, motility, and viability) (Chan et al., 2009; Mahanem et al., 2004; Wahab et al., 2010) and testosterone (Chan et al., 2009) have also been shown in animal models.
- *Hormonal agents*. Eurycomanone, a constituent of *Eurycoma longifolia* had antiestrogenic effects against the 17alpha-ethynylestradiol (EE)-induced uterotrophy of immature rats (Teh et al., 2011). In animal research, *Eurycoma longifolia* increased testosterone levels (Chan et al., 2009).
- *Hypertensives/Hypotensives*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010).
- *Hypoglycemics*. In animal research, *Eurycoma longifolia* reduced blood glucose in hyperglycemic animals (Husen et al., 2004).

- *Immunomodulators*. According to secondary sources, *Eurycoma longifolia* should not be used by people taking immunosuppressant drugs.
- *Osteoporosis agents*. In an aged orchidectomized rat model, *Eurycoma longifolia* had antiosteoporotic (maintaining bone calcium levels) effects (Shuid et al., 2011).
- *Sedatives*. In healthy males, a water-based extract of *Eurycoma longifolia* decreased the bioavailability (by absorption) of propranolol (Salman et al., 2010). In mice, extract fractions of *Eurycoma longifolia* had anxiolytic effects (Ang & Cheang, 1999a; 1999b).

Eurycoma Longifolia/Food Interactions

- Insufficient available evidence.

Eurycoma Longifolia/Lab Interactions

- *Blood glucose*. In animal research, *Eurycoma longifolia* reduced blood glucose in hyperglycemic animals (Husen et al., 2004). According to secondary sources, *Eurycoma longifolia* increased glucose levels in humans.
- *Blood lipids*. According to secondary sources, *Eurycoma longifolia* increased HDL cholesterol levels in humans.
- *Body fat*. In humans, *Eurycoma longifolia* increased fat free mass, reduced body fat, and increased muscle strength and size (Hamzah & Yusof, 2003).
- *Cortisol*. According to secondary sources, *Eurycoma longifolia* decreased cortisol levels in humans.
- *Hormones*. In animal research, *Eurycoma longifolia* increased testosterone levels (Chan et al., 2009; Zanoli et al., 2009). According to secondary sources (unpublished results), *Eurycoma longifolia* increased testosterone and dehydroepiandrosterone (DHEA) levels in humans.
- *Insulin-like growth factor (IGF-1)*. According to secondary sources, *Eurycoma longifolia* modulated the release of IGF-1 in humans, decreasing levels in women.
- *Semen parameters*. In humans, sperm motility significantly increased with use of *Eurycoma longifolia* (Tambi & Imran, 2010). In animal research, *Eurycoma longifolia* improved sperm parameters (sperm count, motility, and viability) (Chan et al., 2009; Mahanem et al., 2004; Wahab et al., 2010).

Eurycoma Longifolia/Nutrient Depletion

- *Blood glucose*. In animal research, *Eurycoma longifolia* reduced blood glucose in hyperglycemic animals (Husen et al., 2004).

MECHANISM OF ACTION

Pharmacology

- *Constituents*. Constituents of the wood, stems, roots, and leaves of *Eurycoma longifolia* include eurycomanone (Chan, Choo, Morita, & Itokawa, 1998; Chan, ONeill, Phillipson, & Warhurst, 1986; Darise et al., 1982; Darise et al., 1983; Low, Ng, Choy, Yuen, & Chan, 2005; Wernsdorfer, Ismail, Chan, Congpuong, & Wernsdorfer, 2009); the quassinoid 13beta,18-dihydroeurycomanol (Chan

et al., 1991); 14,15beta-dihydroxyklaineanone (Chan et al., 1991; Chan et al., 1998; Itokawa et al., 1993); 13alpha,21-dihydroeurycomanone (Teh et al., 2011; Wernsdorfer et al., 2009); the eurycomanone quassinoid 4,5,7,8,17-penta-hydroxy-14,18-dimethyl-6-methyl-ene-3,10-dioxapenta-cyclo-[9.8.0.0.0.0]nona-dec-14-ene-9,16-dione methanol solvate dehydrate (Teh, Teoh, Yeap, Chan, & Fun, 2009); the quassinoid 6alpha-hydroxyeurycomalactone (Chan et al., 1992; Chan et al., 1998; Itokawa et al., 1993); eurycomanol (Chan et al., 1986; Chan et al., 1998; Darise et al., 1982; Darise et al., 1983); eurycomanol-2-O-beta-D-glucoside (Chan et al., 1998); C18 quassinoids (laurycolactones A and B) (Itokawa et al., 1993); 1,2-seco-1-nor-6(5->10)abeo-picrasan-2,5-olide skeleton quassinoids (eurylactones A and B) (Itokawa et al., 1992; Itokawa et al., 1993); C19 skeleton quassinoids (Itokawa et al., 1993); 9,10-dimethoxycanthin-6-one, 10-hydroxy-9- methoxycanthin-6-one, dihydroniloticin, and 14-deacetyleurylene (Miyake, Tezuka, Awale, Li, & Kadota 2010); canthin-6-one alkaloids (4,9-dimethoxycanthin-6-one, 10-hydroxy-11-methoxycanthin-6-one, 9,10-dimethoxycanthin-6-one, 11-hydroxy-10-methoxycanthin-6-one, 5,9-dimethoxycanthin-6-one, and 9-methoxy-3-methylcanthin-5,6-dione) (Miyake et al., 2010; Lin et al., 2011); 10-hydroxycanthin-6-one (Chan et al., 1986); a tirucallane-type triterpenoid, 23,24,25-trihydroxytirucall-7-en-3,6-dione (Miyake et al., 2010); oxasqualenoid (Miyake et al., 2010); biphenylneolignans (2-hydroxy-3,2′,6′-trimethoxy-4′-(2,3-epoxy-1-hydroxypropyl)-5-(3-hydroxy-1-propenyl)-biphenyl and 2-hydroxy-3,2′-dimethoxy-4′-(2,3-epoxy-1-hydroxypropyl)-5-(3-hydroxy-1-propenyl)biphenyl) (Morita, Kishi, Takeya, & Itokawa, 1992); beta-carboline alkaloids (Mitsunaga et al., 1994); 13beta,21-dihydroxyeurycomanol (Kuo, Damu, Lee, & Wu, 2004); eurycomalactone (Chan et al., 1986; Chan et al., 1998; Itokawa et al., 1993; Oei-Koch & Kraus, 1980); 5alpha,14beta,15beta-trihydroxyklaineanone (Kuo et al., 2004); 15beta-acetyl-14-hydroxyklaineanone (Chan et al., 1998); eurycomalides A and B (Kuo et al., 2004); n-pentyl beta-carboline-1-propionate, 5-hydroxymethyl-9-methoxycanthin-6-one, and 1-hydroxy-9-methoxycanthin-6-one (Kuo et al., 2003); eurycomaoside (Bedir, Abou-Gazar, Ngwendson, & Khan, 2003); 9-methoxycanthin-6-one, 3-methylcanthin-5,6-dione, and its 9-methoxy analog (Choo & Chan, 2002; Tan, Yuen, & Chan, 2002); longilactone (Chan et al., 1998; Itokawa et al., 1993); 1beta,12alpha,15beta-triacetyleurycomanone (Chan et al., 1998); C19-skeleton quassinoids, 6-dehydroxylongilactone and 7alpha-hydroxyeurycomalactone (Itokawa et al., 1993; Morita et al., 1993); C20-skeleton quassinoids (Itokawa et al., 1993; Morita et al., 1993); eurycolactone B, eurycolactones D-F, and eurycomalactone (Ang, Hitotsuyanagi, Fukaya, & Takeya 2002); anthraquinones and anthraquinone glucosides (Lin et al., 2011); squalene-type triterpenes (eurylene, 14-deacetyl eurylene, and longilene peroxide), and teurilene (Morita et al., 1993); campesterol, stigmasterol, sitosterol, and saponins (unspecified) (Oei-Koch & Kraus, 1978); pasakbumin-B (based on a review) (Bhat & Karim, 2010); 13alpha(21)-epoxyeurycomanone (Wernsdorfer et al., 2009); 11-dehydroklaineanone; 5,6-dehydroeurycomalactone (Itokawa et al., 1993); tirucallane-type triterpenes (niloticin, dihydroniloticin, piscidinol A, bourjotinolone A, 3-episapelin A, melianone, and hispidone) (Itokawa et al., 1993); 12-epi-11-dehydroklaineanone (Jiwajinda, Santisopasri, Murakami, Hirai,

& Ohigashi, 2001); and others (unspecified) (Kuo et al., 2003; Kuo et al., 2004; Kardono et al., 1991; Le & Nguyen, 1970; Miyake, Tezuka, Awale, Li, & Kadota, 2009; Miyake et al., 2010; Miyake et al., 2010; Mohamad, Li, & Hmad, 2010; Morita et al., 1990; Suppakan & Suriyapananont, 1983). According to secondary sources, constituents include glycoprotein (Tambi & Imran, 2010), aervin, 9-hydroxycanthin-6-one, 9-hydroxycanthin-6-one n-oxide, 9-methooxycanthin-6-one, 9-methooxycanthin-6-one n-oxide, beta-carboline-1-propionic acid, beta-7-methoxycarboline-1-propionic acid, 13-21-dihydroeurycomanone, and 13-beta-21-dihydroxyeurycomanone.

- In cell suspension cultures, the canthin-6-one alkaloids 9-hydroxycanthin-6-one and 9-methoxycanthin-6-one were determined (Aziz, Keng, & Lim, 2009; Lufthi, Chan, & Boey, 2004; Maziah & Rosli, 2009; Rosli et al., 2009).
- Predominant amino acids were alanine, proline, arginine, and serine (Kuo, Damu, & Wu, 2003). A 4.3kDa bioactive peptide was determined in *Eurycoma longifolia* (Asiah, Nurhanan, & Mohd, 2007). *Eurycoma longifolia* is about 39% starch (Lugnataweepon et al., 2011).
- The constituents of *Eurycoma longifolia* were the topic of a review (Hussein et al., 2007).
- Said, Gibbons, & Zloh (2010) described the chemometric analysis of solid herbal products in the development of spectral databases.
- *Antibacterial effects*: Alcoholic, acetone, and aqueous extracts of *Eurycoma longifolia* had antibacterial effects against various Gram-negative and Gram-positive bacteria (Farouk & Benafri, 2007; Reddy et al., 2010). Another study found that *Eurycoma longifolia* lacked an antibacterial or antifungal effect at $\leq$10 and 50 mg/ml of root extract, respectively (Tzar, Hamidah, & Hartini, 2011).
- *Anticancer effects*: In vitro, quassinoid constituents and extracts of *Eurycoma longifolia* were cytotoxic against cancer cell lines (Itokawa et al., 1993; Jiwajinda et al., 2002; Kuo et al., 2003; Miyake et al., 2010; Morita et al., 1993; Nurhanan et al., 2002; Nurhanan et al., 2005). The cytotoxic effects of constituents of *Eurycoma longifolia* were shown in other studies (Kuo et al., 2003), but further details are limited. The antiproliferative activity of *Eurycoma longifolia* was examined, but conclusions are not available at this time (Ueda et al., 2002).
- The cytotoxic activity of quassinoids was not found to be mediated through DNA cleaving properties (Chan et al., 1992). In vitro, the anticancer effects of a fraction of *Eurycoma longifolia* were due to apoptosis via a caspase-9-and p53-independent manner (Tee, Cheah, & Hawariah, 2007) that perhaps involved Bcl-2 protein (Tee & Azimahtol, 2005).
- *Antidiabetic effects*: In animal research, *Eurycoma longifolia* reduced blood glucose in hyperglycemic animals (Husen et al., 2004).
- *Antimalarial effects*: In animal research, parasitemia suppression of *Plasmodium yoelii*-infected mice was shown (Mohd Ridzuan et al., 2007). Ethanol and methanol-ethanol extracts of roots and constituents of *Eurycoma longifolia* had antiplasmodial effects against *Plasmodium falciparum* in culture (Ang et al., 1995; Ang et al., 1995; Hout et al., 2006; Jiwajinda et al., 2002; Sriwilaijaroen et al., 2010). The antimalarial effects of various constituents of *Eurycoma longifolia* were reported against *Plasmodium falciparum* in vitro (Chan et al., 1986;

Chan et al., 1998; Chan, Choo, Abdullah, & Ismail, 2004). In vitro, an extract of *Eurycoma longifolia* affected glutathione levels in noninfected erythrocytes, the trophozoite (*Plasmodium falciparum*)-infected erythrocyte, and the parasite itself, but not the enriched trophozoite-infected erythrocyte (Mohd Ridzuan et al., 2005). Extracts were found to be most potent at the trophozoite stages (Sholikhah, Wijayanti, Nurani, & Mustofa, 2008).

- According to one study, eurycomanol, eurycomanol 2-O-beta-D-glucopyranoside, and 13 beta, 18-dihydroeurycomanol had IC_{50} values of 1.231–4.899, 0.389–3.498, and 0.504–2.343 mcM, respectively, compared with 0.323-0.774 mcM for chloroquine (Ang et al., 1995). The IC_{50} of dehydroklaineanone and 15beta-O-acetyl-14-hydroxyklaineanone was 2 mcg/ml (Jiwajinda et al., 2002).
- The antimalarial effects of constituents of *Eurycoma longifolia* were shown in other studies (Kuo et al., 2003), but further details are limited. Diacylated derivatives synthesized from eurycomanone isolated from *Eurycoma longifolia* had antimalarial effects and had reduced toxicity versus the original compound (Chan, Choo, & Abdullah, 2005).
- *Anxiolytic effects*: In mice, extract fractions of *Eurycoma longifolia* had anxiolytic effects, resulting in decreased fighting and more exploration in an open field test (which measures willingness to explore) (Ang & Cheang, 1999a; 1999b). The extract increased the number of squares crossed in the test and decreased immobility. In the elevated-maze test, the extract increased the number of entries and time spent in open arms and decreased the number of entries and time spent in closed arms (a test of anxiety based on rodents' dislike of open arms).
- *Bone effects*: In an aged-orchidectomized rat model, *Eurycoma longifolia* had antiosteoporotic (maintaining bone calcium levels) effects (Shuid et al., 2011). Hormones related to bone formation were not affected (serum osteocalcin and terminal C-telopeptide type 1 collagen).
- *Ergogenic effects*: The ergogenic effects of *Eurycoma longifolia* were discussed in a review (Muhamad et al., 2009). The authors reviewed its medicinal properties and studies investigating physiological responses and endurance exercise performance. Increased testosterone, as shown in animal models (Chan et al., 2009), has been suggested in anecdotal reports as being responsible for *Eurycoma longifolia*-induced increases in muscle mass and strength in humans. According to secondary sources, *Eurycoma longifolia* enhances testosterone production by the Leydig cells and frees bound testosterone for use by muscles.
- *Fertility effects*: In humans, sperm motility significantly increased with use of *Eurycoma longifolia* (Tambi & Imran, 2010). In animal research, *Eurycoma longifolia* stimulated copulatory behavior in noncopulator, middle-aged, or sexually sluggish and impotent male rats (Ang & Cheang, 1999a; 1999b; Ang & Cheang, 2002; Ang & Lee, 2002; Ang & Ngai, 2001; Ang & Sim, 1998; Zanoli et al., 2009); episodes of penile reflexes in male rats (Ang et al., 2001); aphrodisiac and sexual motivation enhancement effects in sexually naïve male mice (Ang & Sim, 1998; Ang et al., 1997; Ang et al., 2003) and rats (Ang & Sim, 1998); and decreased sexual hesitation in middle-aged rats (Ang et al., 2003). In animal research, *Eurycoma longifolia* fractions increased sexual orientation activities in middle-aged

male rats (Ang & Lee, 2002) and sexual orientation activities and mounting frequency in sexually experienced male rats (Ang & Sim 1997; Ang & Sim, 1998). Orientation activities toward the receptive females were increased with respect to anogenital sniffing, licking, and mounting. As well, they showed increased genital self-grooming and had decreased interest in the external environment (climbing, raring, exploration). In inexperienced castrated male rats, *Eurycoma longifolia* extracts resulted in increased sexual performance and growth of ventral prostate and seminal vesicles (although lower than in a testosterone-treated group) (Ang, Cheang, & Yusof, 2000). In male rats, *Eurycoma longifolia* improved sexual performance by extending the duration of coitus and decreasing the refractory period between copulation series (Ang et al., 1997). Improved sperm parameters (sperm count, motility, and viability) (Chan et al., 2009; Mahanem et al., 2004; Wahab et al., 2010) and testosterone (Chan et al., 2009) have also been shown in animal models.

- In male rats, *Eurycoma longifolia* increased pandiculation activities (simultaneous yawing and stretching); the authors indicated that this supports its aphrodisiac effects (Ang, Lee, & Kiyoshi, 2004; Ang & Sim, 1998).
- In animal research, an herbal combination containing *Panax quinquefolius*, *Eurycoma longifolia*, *Epimedium grandiflorum*, *Centella asiatica*, and flower pollen extracts enhanced erectile function (Qinna et al., 2009). Improvements were noted in the penile erection index (PEI). In boars, an herbal preparation containing *Eurycoma longifolia*, *Tribulus terrestris*, and *Leuzea carthamoides* increased libido by 20% and semen quality (volume, concentration, etc.) (Frydrychova et al., 2011).
- The aphrodisiac effects of *Eurycoma longifolia* and other herbs have been discussed in a review (Malviya, Jain, Gupta, & Vyas, 2011). Further details are lacking at this time.
- *Hormonal effects*: Eurycomanone, a constituent of *Eurycoma longifolia*, had antiestrogenic effects against 17alpha-ethynylestradiol (EE)-induced uterotrophy of immature rats (Teh et al., 2011).
- *Insecticidal effects*: *Eurycoma longifolia*-containing smoke from mosquito coils resulted in increased knock-down activities of mosquitos, but not increased mortality (Jantan et al., 1999).
- *Muscular effects*: In animal research, *Eurycoma longifolia* extracts increased weight of the levator ani muscle (involved in tail wagging) in castrated animals, but not testosterone-treated animals and uncastrated animals (Ang & Cheang, 2001).

Pharmacodynamics/Kinetics

- *Absorption*: The bioavailability of the constituent eurycomanone was investigated in animal research (Low et al., 2005). Following intravenous injection, eurycomanone was detected in the plasma, declining to zero within 8 hr. Following oral administration, C_{max} and T_{max} values were 0.33 ± 0.03 mcg/ml and 4.40 ± 0.98 hr, respectively. The plasma concentration was lower following oral administration versus intravenous administration, even at a much higher oral dose

(five times the dose). The authors concluded that eurycomanone is poorly bioavailable orally (10.5%).

- In animal research, less than 1% of the constituent 9-methoxycanthin-6-one was found to be absorbed orally (Tan et al., 2002).
- Following oral administration of a standardized extract (Fr 2) of *Eurycoma longifolia*, 13alpha(21)-epoxyeurycomanone had a higher C_{max} than eurycomanone (1.61 ± 0.41 mcg/ml vs. 0.53 ± 0.10 mcg/ml) (Low, Teh, Yuen, & Chan, 2011). The absolute bioavailability was also higher due to increased membrane permeability (higher log Kow value of –0.43 vs. –1.46 at pH 1). Following oral administration of a standardized extract (Fr 2) of *Eurycoma longifolia*, eurycomanol and 13alpha,21-dihydroeurycomanone were not detected in plasma (Low et al., 2011).
- *Distribution*: In animal research, the volume of distribution (V(d)) of eurycomanone was relatively high (0.68 ± 0.30 l/kg), suggesting that it is well distributed in the extravascular fluids (Low et al., 2005).
- ***Excretion***: Following intravenous injection, the mean elimination rate constant (k(e)) and clearance (CL) for eurycomanone were 0.88 ± 0.19 hr (–1) and 0.39 ± 0.08 l/hr/kg, respectively (Low et al., 2005).
- *Half-life*: Following intravenous administration of a standardized extract (Fr 2) of *Eurycoma longifolia*, 13alpha(21)-epoxyeurycomanone had a longer biological half-life than eurycomanone (0.75 ± 0.25 hr vs. 0.35 ± 0.04 hr), due to a lower elimination rate constant (Low et al., 2011). Conversely, another study reported the biological half-life (t(1/2)) of eurycomanone to be 1.00 ± 0.26 hr (Low et al., 2005).
- *Measurement*: Tan et al. (2002) described an HPLC analysis of plasma 9-methoxycanthin-6-one from *Eurycoma longifolia* following injection. Low et al. (2011) described an LC-UV method for the analysis of 13alpha(21)-epoxyeurycomanone, eurycomanone, 13alpha,21-dihydroeurycomanone, and eurycomanol in rat plasma following oral and intravenous administration of a standardized extract (Fr 2) of *Eurycoma longifolia*.

HISTORY

- *Eurycoma longifolia* (tongkat ali) has a long history of use in Malaysia as an aphrodisiac, as well as for its antipyretic, antimalarial, antidiabetic, and antimicrobial properties.
- Vittachi (1994) discussed reports that suggest that world leaders are using *Eurycoma longifolia* . They also suggest that the Malaysian president gave a gift of *Eurycoma longifolia* to the U.S. president. In a report by Cyranoski (2005), it is suggested that successful studies on *Eurycoma longifolia* are yet unpublished because of intellectual property concerns .
- According to secondary sources, *Eurycoma longifolia* has been protected in Malaysia since the early 21st Century and cannot be harvested from the wild.

EVIDENCE TABLE

Condition Treated	Study Type	Author, Year	*N*	Statistically Significant Results?	Quality of Study: 0–2 = poor, 3–4 = good, 5 = excellent	Magnitude of Benefit (How Strong is the Effect?)	Absolute Risk Reduction	# of Patients Needed to Treat for One Outcome	Comments
Athletic endurance	Randomized controlled trial; crossover design	Muhamad, 2010	12	No	2	NA	NA	NA	No effect on endurance running capacity in healthy male recreational athletes.
Enhanced muscle mass/strength	Randomized controlled trial	Hamzah, 2003	14	Unclear	1	NA	NA	NA	Study published in abstract form only.
Male fertility	Open trial	Tambi, 2010	350	Yes (semen parameters vs. baseline)	NA	Medium	NA	NA	Large numbers of noncompleters. Improved sperm count.

Explanation of Columns in Natural Standard Evidence Table

1	2	3	4	5	6	7	8	9	10
Condition	Study design	Author, year	*N*	Statistically significant?	Quality of study 0–2 = poor 3–4 = good 5 = excellent	Magnitude of benefit	Absolute risk reduction	Number needed to treat	Comments

Condition

- Refers to the medical condition or disease targeted by a therapy.

Study Design

Common types include:

- *Randomized controlled trial (RCT)*: An experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines RCTs as being placebo-controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.
- *Equivalence trial*: An RCT which compares two active agents. Equivalence trials often compare new treatments to usual (standard) care, and may not include a placebo arm.
- *Before and after comparison*: A study that reports only the change in outcome in each group of a study, and does not report between group comparisons. This is a common error in studies that claim to be RCTs.
- *Case series*: A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterwards). Case series are considered weak evidence of efficacy.
- *Case-control study*: A study in which patients with a certain outcome are selected and compared to similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary & alternative medicine literature.
- *Cohort study*: A study which assembles a group of patients with certain baseline characteristics (for example, use of a drug), and follows them forward in time for outcomes. This study design is not common in the complementary & alternative medicine literature.
- *Meta-analysis*: A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone but in aggregate can achieve significance). Multiple difficulties are encountered when designing/reviewing these analyses; in particular, outcomes measures or therapies may differ from study to study, hindering direct comparison.
- *Review*: An author's description of his or her opinion based on personal, nonsystematic review of the evidence.
- *Systematic review*: A review conducted according to prespecified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.

Author, Year

- Identifies the study being described in a row of the table.

N

- The total number of subjects included in a study (treatment group plus placebo group). Some studies recruit a larger number of subjects initially, but do not use them all because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as N, which includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of dropouts that are not included in the analysis are considered to be weaker evidence for efficacy. For systematic reviews, the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.

Statistically Significant?

- Results are noted as being statistically significant if a study's authors report statistical significance, or if quantitative evidence of significance is present (such as *p* values). *P* = pending verification.

Quality of study

- A numerical score between 0–5 is assigned as a rough measure of study design/reporting quality (0 being weakest and 5 being strongest). This number is based on a well-established, validated scale developed by Jadad et al. (1996). This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the "Evidence Discussion" sections of reviews).
- A Jadad score is calculated using the seven items in the table below. The first five items are indications of good quality, and each counts as one point towards an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0 to 5.

Jadad score calculation

Item	Score
Was the study described as randomized (this includes words such as randomly, random, and randomization)?	0/1
Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc)?	0/1
Was the study described as double blind?	0/1
Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc)?	0/1
Was there a description of withdrawals and dropouts?	0/1
Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc).	0/–1
Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).	0/–1

Magnitude of Benefit

- This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant "NA" for "not applicable" is entered. In order to be consistent in defining small, medium, and large benefits across different studies and reviews, Natural Standard defines the magnitude of benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered:
  - Large: if >1 SD
  - Medium: if 0.5 to 0.9 SD
  - Small: if 0.2 to 0.4 SD
- In many cases, studies do not report the standard deviation of change of the outcome measure. However, the change in the standard deviation of the outcome measure (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled standard deviation (Effect size = [Mean Treatment – Mean placebo]/SDp).

Absolute Risk Reduction

- This describes the difference between the percent of people in the control/placebo group experiencing a specific outcome (control event rate), and the percent of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, Absolute risk reduction (ARR) equals experimental event rate minus control event rate. ARR is better able to discriminate between large and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies ([control event rate – experimental event rate]/control event rate). Many studies do not include adequate data to calculate the ARR, in which cases "NA" is entered into this column. *P* = pending verification.

Number Needed to Treat

- This is the number of patients who would need to use the therapy under investigation, for the period of time described in the study, in order for one person to experience the specified benefit. It is calculated by dividing the Absolute Risk Reduction into 1 (1/ARR). *P* = pending verification.

Comments

- When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, not intention-to treat, etc.), notable study design elements (crossover, etc.), dosing, and/or specifics of study group/subgroups (age, gender, etc). More detailed description of studies is found in the "Evidence Discussion" section that follows the "Evidence Table" in Natural Standard reviews.

EVIDENCE DISCUSSION

Athletic Endurance

- *Summary*: Preliminary evidence suggests a lack of effect of *Eurycoma longifolia* on endurance in humans. However, the available information is limited, and further research is needed before conclusions can be made.
- *Evidence*: Muhamad et al. (2010) conducted a randomized controlled and crossover trial to determine the effects of *Eurycoma longifolia* Jack on endurance running capacity and physiological responses in the heat in 12 male recreational athletes. The subjects exercised for at least 30 min per session and at least twice per week prior to the study. Other inclusion and exclusion criteria were not provided. Twenty-four hours prior to testing, subjects were to refrain from strenuous exercise and from other sources of *Eurycoma longifolia*. Subjects were randomized to order of placebo and *Eurycoma longifolia* (2 × 75 mg capsules) (similar in size and color). The method of randomization was not indicated. All subjects underwent a familiarization run. The products were taken for seven days prior to, and 1 hr before, an endurance running trial (31°C, 70% relative humidity), performed on separate days. On the day of the trial, subjects warmed up at 50% of VO_2max, followed by a run at 60% of VO_2max for 60 min. Then, the subject ran for 20 min, with the goal to run the longest distance possible during that time. The primary endpoint was not indicated. Endpoints included oxygen uptake, skin temperature, heart rate, blood biochemistry, and endurance running capacity. The authors found a lack of significant differences between placebo and *Eurycoma longifolia* for any of the endpoints (including lab parameters of ratings of perceived exertion, hemoglobin concentration, hematocrit level, plasma glucose concentration, and plasma free fatty acid concentration). Adverse effects were not discussed. This study is limited by the lack of description of randomization and blinding (it is unclear if the products were identical). Also, although the endpoint was endurance running capacity, in fact the speed during the last 20 min was determined, not the actual time able to run.

Enhanced Muscle Mass/Strength

- *Summary*: Preliminary research suggests that *Eurycoma longifolia* increases muscle mass in individuals also undergoing a strength program. Researchers suggest that increased testosterone levels are responsible for these effects, although published clinical research on testosterone levels is lacking in humans. Further research is required.
- *Evidence*: Hamzah and Yusof (2003) conducted a randomized controlled pilot study to examine the effects of *Eurycoma longifolia* Jack on muscle strength and mass in 14 healthy men. This study was published in abstract form; thus, details are limited. Inclusion and exclusion criteria were lacking. The men also performed an intense strength training program for five weeks. Subjects were randomized to placebo or extract (100 mg daily) for those same five weeks. The authors indicated that *Eurycoma longifolia* increased fat free mass, reduced body fat, and increased muscle strength and size. This study is limited by the lack of overall detail.

- *Select combination study (not included in the Evidence Table)*: Sareena & Ashril (2002) conducted a study to examine the effects of a combination of a water-soluble extract of *Eurycoma longifolia* and training on changes in muscular mass, muscle strength, and muscle activity in six men. This study was published in abstract form, so details are limited. Inclusion and exclusion criteria were not provided. The men performed an intense strength training program and consumed 50 mg of the *Eurycoma longifolia* water extract and 300 mg of lactose. All participants were also advised not to consume any supplements or androgenic steroids throughout the exercise regime. Endpoints included muscle changes. Muscle circumference increased from 30.7 ± 1.8 cm to 32.1 ± 2.2 cm ($p < .05$). The authors indicated that there was a slight increase in the repeated measures (RM) test and that surface electromyography (sEMG) muscle contraction showed slight increment. The authors indicated that the study is limited by the number of subjects, which was determined following dropouts, and by errors in generating meaningful data.

Male Fertility

- *Summary*: In animal research (Ang & Cheang, 1999a; 1999b; Ang & Cheang, 2002; Ang & Lee, 2002; Ang & Ngai, 2001; Ang & Sim, 1998; Ang & Sim, 1998; Ang & Sim, 1998; Ang et al., 1997; Ang et al., 2001; Ang et al., 2003; Ang et al., 2003; Zanoli et al., 2009) and according to anecdotal evidence in humans, *Eurycoma longifolia* increases sexual desire and coitus attempts, as well as testosterone levels. Further well-designed research in humans is required before conclusions can be drawn.
- *Evidence*: Tambi & Imran (2010) conducted an open study in order to determine the effect of *Eurycoma longifolia* Jack on sperm parameters in 350 patients with idiopathic male infertility. Inclusion and exclusion criteria were not specified. Patients took two capsules orally of 100 mg of a proprietary standardized water-soluble extract of *Eurycoma longifolia* Jack root (U.S. Patent: US7,132,117B2 from Phytes Bioteks, Biotropics Malaysia, Berhad, Malaysia), twice daily after eating. Patients were followed every three months for three cycles (nine months). The main endpoint was semen analysis. Of the 350 patients, 75 completed one full cycle of three months, 49 completed two cycles, and 17 completed three cycles. In these patients, semen analyses showed significant improvement in all semen parameters (sperm concentration, normal sperm morphology) ($p < .05$). Sperm motility significantly increased after the first cycle only ($p = .037$). The authors indicated that 11 spontaneous pregnancies occurred (14.7%). Adverse effects were not discussed. This study is limited by the lack of randomization, control, and blinding.

BRANDS USED IN CLINICAL TRIALS/THIRD-PARTY TESTING

- Not applicable.

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