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File: ■ Tongkat Ali (*Eurycoma longifolia*, Simaroubaceae)
■ Erectile Dysfunction
■ Toxicology
■ Review

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RE: Beneficial Bioactivities of Tongkat Ali Are Diverse and May Include Treatment of Erectile Dysfunction

Rehman SU, Choe K, Yoo HH. Review on a traditional herbal medicine, *Eurycoma longifolia* Jack (Tongkat Ali): Its traditional uses, chemistry, evidence-based pharmacology and toxicology. *Molecules*. March 2016;21(3):331. doi: 10.3390/molecules21030331.

Eurycoma longifolia (Simaroubaceae), known traditionally as Tongkat Ali, is a shrubby tree native to Southeast Asia, Malaysia, and Indonesia. Traditionally, water decoction of the root is consumed as a tonic or adaptogen, as a panacea for a wide variety of discomforts, and to treat conditions including malaria, sexual dysfunction, cancer, and diabetes. Currently, the raw crude root powder is consumed. There are several categories of bioactive components, but quassinoids are the most numerous. The quantity of quassinoids measured via liquid chromatography-mass spectrometry (LC-MS) can be used to confirm purity of Tongkat Ali and for product identification. This review article describes the uses of Tongkat Ali and the scientific evidence supporting its use. This review includes many references, and each scientific study is described very briefly. As a consequence, this HerbClip summarizes the data with equal brevity.

Tongkat Ali is used to enhance male fertility. Studies in rats demonstrate that Tongkat Ali increases semen volume, spermatogenesis, spermatozoa count and motility, testosterone steroidogenesis in Leydig cells, plasma testosterone levels, penile reflexes, and sexual behavior including mounting and ejaculation, and decreases hesitation time.

The authors describe six clinical trials and one meta-analysis that evaluated Tongkat Ali for related uses in men. Three randomized, placebo-controlled, human trials (RCTs) evaluated a proprietary freeze-dried water extract (Physta®; Biotropics Malaysia Berhad; Selangor, Malaysia). In one study, men (n = 109; aged 30-55 years) were treated with 300 mg Physta or placebo for 12 weeks. The Physta group had improvements in overall erectile function scores ($P < 0.001$), a 14% increase in libido, a 44.4% increase in sperm motility, and an 18.2% increase in semen volume. It is unclear whether these increases are compared with baseline or placebo. In the second RCT, male recreational athletes

(number and age not reported [NR]) were treated with 400 mg/day Physta or placebo for six weeks. There were no significant differences between groups in the ratio of testosterone:epitestosterone, liver function, or renal function. In the third RCT, healthy men (n = NR; aged 40-65 years) were treated with Physta (dose NR) or placebo for 12 weeks. Sexual intercourse attempts, erection quality, and measures of sexual health and "aging male symptom[s]" improved more in the Physta group ($P < 0.05$ for all). Physta was well tolerated. A meta-analysis of RCTs of Tongkat Ali compared to placebo concluded that current evidence supports a clinical effect on erectile dysfunction, but a recommendation for its use could not be made without additional research.

An open-label study of men (n = 350; age NR) treated with 200 mg/day Tongkat Ali (duration NR) analyzed semen every three months up to nine months. Unspecified semen parameters improved, and there were 11 spontaneous pregnancies [stated without explanation to be "14.7%"]. In a second study, men with late-onset hypogonadism were treated with Tongkat Ali (dose and duration NR). Patients had a significant improvement in the Ageing Males' Symptoms score and serum testosterone concentration compared with baseline ($P < 0.0001$). In a pilot study, physically active men and women (n = NR; aged 57-72 years) were treated with 400 mg/day Tongkat Ali for five weeks to evaluate its ergogenic effect (enhancing physical performance) in elderly people. Muscle strength improved and total and free testosterone concentrations increased in men and women compared with baseline (P values not given).

Tongkat Ali has dose-dependent activity in vitro against *Plasmodium falciparum*, which causes malaria. The quassinoids may contribute to the activity; synergy among multiple active compounds is apparent. No human or animal studies were reported.

In vitro, Tongkat Ali root extracts or fractions are cytotoxic and antiproliferative in human cancer cell lines, including lung, breast, colon, and cervical cancers, melanoma, fibrosarcoma, and epidermoid carcinoma of the nasopharynx. In particular, the compounds 9-methoxycanthin-6-one and canthin-6-one were most cytotoxic against human lung and breast cancer cell lines, and one fraction caused apoptosis (cell death) in breast cancer cells. The compound eurycomanone caused apoptosis in an ovarian cancer cell line. Eurycomanone and eurycomanol can regulate signaling pathways involved in proliferation, cell death, and inflammation. Fractions of the root extract show activity against acute promyelocytic leukemia and chronic myelogenous leukemia, the latter also in vivo. Tongkat Ali did not have significant cytotoxic effects on normal/healthy cell lines. In vivo, it is reported to inhibit subcutaneous tumor growth and angiogenesis.

Alcoholic and acetone extracts of the leaves and stems, but not the roots, have activity against the Gram-negative bacteria *Escherichia coli* and *Salmonella typhi*. Aqueous leaf extract had activity against *Staphylococcus aureus* and *Serratia marcescens*. The beta-carboline alkaloids of Tongkat Ali produced anti-inflammatory activity in vitro. A hydroalcoholic extract had antioxidant activity (free radical scavenging) in vitro, and dose-dependent inflammatory activity.

The antianxiety effects of fractions of Tongkat Ali were compared with the positive control diazepam in vivo. The fractions had similar antianxiety effects as diazepam in multiple tests in rats. In an RCT, subjects (n = 63; age NR) with moderate stress were treated with a hot-water extract of Tongkat Ali (dose NR) or placebo daily for four weeks. *Eurycoma longifolia* improved stress hormone levels and "certain mood state parameters" (no additional details were provided).

In diabetic rats, but not normoglycemic rats, two aqueous extracts of Tongkat Ali decreased blood glucose levels by 38% and 47% ($P < 0.05$ and $P < 0.001$, respectively). In vitro, root extract increased insulin sensitivity and glucose uptake and suppressed lipid accumulation dose-dependently.

In vivo, Tongkat Ali prevented bone calcium loss in orchidectomised rats. Thus, it has a potential use for androgen-deficient osteoporosis in men. Its testosterone-enhancing effects can stimulate osteoblast proliferation and differentiation, increasing the bone formation rate. Androgen-deficient osteoporosis is treated with testosterone, which can have unwanted side effects. The authors suggest that future studies can evaluate Tongkat Ali plus a lower dose of testosterone to see if the combination can reduce side effects while maintaining efficacy.

Several miscellaneous effects have been reported. An extract of Tongkat Ali normalized irregular estrous cycles and reduced testosterone-induced ovarian follicular damage in rats. Tongkat Ali in smoke from mosquito coils increased mosquito knockout but not death. In vivo, Tongkat Ali increased the weight of the levator ani muscle (involved in tail wagging) in castrated animals. In vitro and in vivo studies have reported that it can inhibit gastric ulcers.

A few of the active compounds, including eurycomanone and 9-methoxycanthin-6-one, are reported to have poor oral bioavailability. Eurycomanone does not inhibit liver cytochrome P450 (CYP) enzymes, which are involved in drug/herb metabolism. However, Tongkat Ali has a weak, concentration-dependent inhibitory effect on CYP1A2, CYP2A6, and CYP2C19 isozymes in vitro. The authors state that caution should be advised when taking extracts with conventional drugs. [Note: However, false positives with such in vitro assays are common.]

Despite historical use, the safety of Tongkat Ali has been formally assessed only since the late 1990s. The composition of ethanolic, n-butanolic-, and aqueous-based fractions differs; consequently, the safety of each differs as well. The water-based fraction is considered the safest, with a Lethal Dose 50 (LD_{50}) in rats of >3000 mg/kg body weight; another study reports an LD_{50} of >6 g/kg. In rat models, the aqueous extract Physta did not produce histopathological changes or acute toxicity after 90 days of treatment at doses of 250-2000 mg/kg/day. A quassinoid-rich extract was used in a two-generation reproductive toxicity study; no negative effects on fetuses were seen, and treated rats had larger litters than controls.

One study calculated the acceptable daily intake for adult humans to be up to 1.2 g/day, based on the levels seen to be harmless in rats; however, the type of extract used in that study was not specified. In humans, 400 mg/day Physta for six weeks did not produce any toxicity to liver or kidney function. Tongkat Ali is considered safe in the usually recommended doses of 200-400 mg daily. The Endocrine Society recommends that men with prostate cancer avoid testosterone treatment. Since Tongkat Ali increases testosterone levels, it may have hypothetical risks for elderly men, who frequently have undetected indolent prostate cancers. It should also be used with caution in patients taking hypoglycemic agents and in patients with weak immune systems. This review suggests that it should be avoided by pregnant or lactating women (due to lack of research in humans). It quotes secondary sources as claiming that use should be avoided by people who have "breast cancer, prostate cancer, heart disease, kidney

disease, liver disease, or sleep apnea … .," though there seems to be no specific rationale for most of these warnings.

The authors acknowledge that more research is needed to evaluate efficacy. The research to date can be viewed as a basis to help guide future in vivo and clinical studies. The authors also suggest that Tongkat Ali could be a valuable source of lead compounds for drug development.

—Heather S. Oliff, PhD

Referenced article can be accessed at http://www.mdpi.com/1420-3049/21/3/331.