# Nutrients and Botanicals to Support Hormonal Metabolism, Anabolic Reserves & Neuroendocrine Restoration

Co-authored by Donald R. Yance, RH (AHG), CN and Suzanne E. Sky, L.Ac., MTOM

# Discussion

# HEALTHY AGING AND ANABOLIC RESERVE

It is vitally important to restore healthy hormonal and metabolic balance for our well-being. Our modern world and the natural aging process continually challenge our bodies with overwhelming stress factors from internal and external sources. This ongoing process can contribute to suboptimal hormone levels and dysfunctional metabolic pathways. Therefore, it is essential to support key components of the biological aging process by protecting the cardiovascular system, supporting anabolic pathways in rebuilding healthy muscle tissue, and balancing overall endocrine function naturally through hormone modulation.

Supporting the anabolic aspect of metabolism is vital to healing and repair, healthy aging, and energy for both daily life and endurance sports. This is because the anabolic process of metabolism is what ensures a healthy storage and reserve of nutrients for use by cells and tissues. Anabolic activity builds and maintains healthy, lean muscle mass. Catabolic activity breaks down nutrients into energy the cells and body can use to function well. In health, anabolic activity predominates over catabolic activity and one measure of such activity is healthy muscle mass and good recovery time from injury, illness, and athletic activity.

#### HEALTHY AGING AND HORMONAL BALANCE

The specific nutrient and botanicals discussed in this paper influence the hormonal system primarily through supporting healthy levels of naturally-occurring human growth hormone, testosterone, dopamine, and DHEA. All of these hormones are implicated in supporting a healthy anabolic reserve along with energy, stamina and endurance.

#### Human Growth Hormone (hGH)

Human growth hormone (hGH) is a master hormone with a regulatory role in basal metabolism that influences body

# Metabolism at Night

During the day, our body's energy is focused on meeting the demands of our daily activities. At night, while we rest, our body does restorative work, including hormonal modulation, cellular repair, and anabolic activity. Our liver metabolism is active, making nighttime optimal for taking specific botanical and nutritional compounds that support the body to work more efficiently.

composition. It promotes healthy muscle development and metabolism of fat and carbohydrates, particularly at night. The intrinsic release of hGH declines significantly after adolescence, which often manifests as diminished resistance to illness, negative changes in sleep patterns, and lower vitality with extended recovery time. There may be loss of muscle mass concurrent with an increase in fat. Key nutrients can enhance hGH levels during the night when levels should peak.

#### Testosterone

Since low levels of free-testosterone are implicated in cardiovascular disease in both men and women, it is likely that an optimal range of testosterone contributes to the maintenance of cardiovascular health.<sup>1,2</sup> According to a recent study, low androgen levels in men correlate with increased risk of atherosclerosis.<sup>3</sup> In another study, depressed levels of both testosterone and sex-hormone-binding globulin (SHBG) correlated with an increased incidence of carotid atherosclerosis. Higher levels of testosterone and SHBG were associated with lower incidence.<sup>4</sup>



In older men, lower total testosterone is associated with insulin resistance and can occur independently of measures of central obesity.<sup>5</sup> Studies find that serum testosterone is markedly decreased in obese males and that a low testosterone to high estrogen ratio can cause an increase in fat storage. The testosterone to estrogen shift is due in part to a reduction in SHBG. Low SHBG levels allow for more peripheral conversion of testosterone to estradiol, which leads to fat accumulation and loss of lean muscle. A reduction in SHBG is also associated with hyperinsulism and insulin resistance.

#### Dopamine

Dopamine is vital as both a brain neurotransmitter and as a hormone, and plays a key role in learning, cognition, and emotion. It regulates motor control, sex drive, immune function, IGF-1 levels, somatotropin release, and motivational behavior. Dopamine is involved with regulation of electrolyte balance in the kidneys, with healthy blood pressure and helps regulate growth hormone levels. Low dopamine levels in the brain hinder the ability of the HPA (hypothalamic-pituitaryadrenal) axis to stimulate testosterone release in men and women.

#### DHEA (Dehydroepiandrosterone)

DHEA is a vital endogenous steroid hormone normally produced in the adrenal glands, gonads, and brain. As a precursor for all the major sex hormones including estrogen, progesterone, and testosterone, it is sometimes referred to as the "mother hormone". It also supports healthy metabolism and anabolic reserves. DHEA naturally declines with aging and the stress of modern-day life, which influences our energy levels, stamina, mood, and sense of well-being.

# Nutrients and Botanicals to Support Hormonal Metabolism, Anabolic Reserves & Neuroendocrine Restoration

#### L-Arginine and L-Citrulline

Arginine, a semiessential amino acid, is widely known for its positive influence on cardiovascular, hormonal, and sexual health. It plays a role in the anabolic process, tissue healing, immune function, and supports healthy recovery time. In numerous studies, arginine is seen to be a consistent and potent stimulus to release hGH.<sup>6</sup> Arginine influences hGH release indirectly, by decreasing the ability of the peptide hormone somatostatin to inhibit the release of hGH, which then leads to an increase of hGH in the body.<sup>7</sup>

L-arginine is converted in the body to nitric oxide (NO), a widely studied compound. Since NO influences cell regulation, it also has a positive impact on healing cellular damage, tendons, intestinal mucosa, and other areas.<sup>8, 9</sup> NO mediates smooth muscle relaxation, promotes vasodilation, and restores vascular tone, which encourages blood flow and vascular health. It supports endothelial function and helps to prevent excess platelet aggregation. Arterial stiffness, one of the main predictors of cardiovascular disease, is regulated by numerous factors including the amount of NO in the vascular endothelium. Too little NO is correlated with increased incidence of hypertension, atherosclerosis, and with diabetic vascular disease.

Because of its conversion to NO, supplementation with

L-arginine helps improve the clinical symptoms of various diseases associated with vascular dysfunction.<sup>10</sup> Enhancing NO function also benefits sexual and erectile function through its effects improving arterial relaxation and blood flow without adverse side effects.<sup>11</sup> L-arginine is also shown to improve female sexual health, including the enhancement of sexual desire.<sup>12</sup>

Current research shows that absorption of oral arginine is limited in some people by metabolic factors. As a precursor of arginine, the amino acid citrulline is well-absorbed while safely and directly raising plasma levels of arginine. Taken together with arginine, citrulline supports healthy plasma arginine levels, flow-mediated vasodilation, and other cardiovascular markers.<sup>13</sup> Both citrulline and arginine contribute directly to healthy levels of NO, which promotes arterial relaxation, elasticity, and resilience.<sup>14</sup>

#### Epimedium sagittatum

Epimedium is a powerful herb with an ancient history that is being highly researched in modern

times. Famously known as "horny goat weed", Epimedium has long been used as an aphrodisiac to enhance both sexual energy and erectile function. The famous Chinese herbal book of remedies, *Shennong Ben Cao Jing*, written around 1200 BC, describes the use of Epimedium for impotence. In modern times it has been found clinically



useful for impotence, fatigue, low sperm count, low libido, spermatorrhea, and sterility.<sup>15</sup>

Known as Yin Yang Huo in Chinese medicine, Epimedium is traditionally combined with other herbs to ameliorate its strong action as Kidney Yang tonic. Valued to support energy, youthful vigor, and a healthy libido, Epimedium is most often included in longevity tonics, such as the famous Two Immortals formula.

Modern research finds that Epimedium supports neurological balance as it modulates catecholamine production and has a normalizing effect on the HPA axis.<sup>15</sup> This is one reason that Epimedium is found useful in cerebral deficiency with memory loss, depression, hormonal deficiency, fatigue impotence, low sperm count, and sexual disinterest.<sup>15</sup> Epimedium flavonoids are found to possess the ability to influence profound regeneration of the adrenocortical pathways with HPA axis dysfunction and to assist HPA axis response and hormonal recovery after long-term stress or glucocorticoid exposure. <sup>16, 17</sup>

Epimedium supports androgenic balance.<sup>18</sup> In several studies, Epimedium extract was found to increase muscle function and integrity and to support health and vigor.<sup>19</sup> The cardiovascular system benefits from Epimedium as it is found to reduce vascular resistance, which supports healthy blood flow. Epimedium has demonstrated anabolic and bone protective effects. Many studies find that Epimedium supports healthy bones through several pathways including promoting bone formation and mineral content; contributing to both bone density and architecture.<sup>20, 21</sup>

Flavonoids are one of the active constituents of Epimedium along with polysaccharides, natural sterols, and fatty acids. Icariin is considered to be the key flavonoid in Epimedium. Both Epimedium and icariin are found to be protective against oxidative stress at the cellular level, supporting healing and repair of aging cells.<sup>20-24</sup>

#### Mucuna pruriens



Natura recommends using a standardized extract of Mucuna

with at least 40% L-dopa.<sup>25</sup> Highly valued in Ayurvedic medicine for centuries, multiple studies confirm the beneficial effects of using *Mucuna pruriens* for nervous system disorders including Parkinson's.<sup>26,27</sup> In Brazil, the seed has been used internally for Parkinson's disease, edema, impotence, and is considered a diuretic, nerve tonic, and aphrodisiac. *Mucuna pruriens* possesses antioxidative and anti-diabetic effects which can help slow the progression of neurological diseases.<sup>28,29</sup>

L-dopa has been used successfully to treat anorgasmia, both in men and women, but particularly in women. With a long folkloric history of being used as an aphrodisiac, modern clinical studies in India have validated that Mucuna has aphrodisiac activity.<sup>30,31</sup>

*Mucuna pruriens* is popular in the field of sports nutrition as it demonstrates the ability to increase growth hormone and testosterone, thus supporting anabolic activity and healthy muscle mass.

#### Tribulus terrestris

Tribulus terrestris has been widely used and revered in Greek, Ayurvedic, and Chinese medicine for thousands of years. In modern times, *Tribulus terrestris* has been used by both Soviet and Bulgarian athletes and bodybuilders as a safe alternative to anabolic steroids because of the anabolic effects of its natural steroidal saponins. Studies confirm its benefit in supporting healthy muscle mass along with athletic performance and endurance.

Protodioscin, a component of Tribulus fruit, is a precursor to DHEA, a vital endogenous steroid hormone normally produced in the adrenal glands, gonads, and brain. DHEA is often depleted with aging and the stress of modern-day life, which influences our energy levels, stamina, mood, and sense of well-being. Studies indicate that Tribulus extract with a minimum concentration of 15% protodioscin is optimal.<sup>32,33</sup> *Tribulus terrestris* extract with 15% protodioscin was clinically proven to improve sexual desire and enhance erection, attributed in part to the conversion of protodioscin to DHEA.<sup>33</sup>

Studies demonstrate that *Tribulus terrestris* increases luteinizing hormone (LH), which stimulates the release of testosterone.<sup>34</sup> One study conducted with 200 males suffering from impotence showed an increase in LH and testosterone levels after supplementing with Tribulus. In addition, many found an increase in libido, sperm production, and in frequency and strength of erections.<sup>35</sup> Another study depicts its ability to enhance serum concentrations of free testosterone and prevent the formation of dihydrotestosterone and estrogens from ingested androgens.<sup>36</sup> Tribulus is also found to improve libido in women, where it can support the release and healthy levels of follicle-stimulating hormone and estradiol.



With benefits on overall health, Tribulus is also found to reduce high blood pressure, decrease elevated lipid levels, regulate insulin levels and improve vasodilation.37



#### Eurycoma longifolia

Eurycoma, often called Malaysian ginseng, enhances athletic performance as well as sexual desire and performance. Over 65 active compounds

have been identified in this ancient medicinal plant known for a wide range of health-promoting benefits. Eurycoma offers a healthy, natural alternative for athletes desiring to increase testosterone levels. It can support healthy aging, muscle mass, and libido in both men and women.

Safely used for thousands of years in Southeast Asian traditional medicine, Eurycoma is one of the most efficacious botanicals for use as an herbal aphrodisiac. Root extracts of Eurycoma are found to have profound aphrodisiacal properties with the ability to reduce fatigue through supporting healthy energy levels. Its influence on sexual desire is thought to correlate with its ability to increase testosterone levels. A recent study found that Eurycoma extract possesses anabolic, androgen-enhancing activity.38-47

One mechanism responsible for the effects of Eurycoma may involve its ability to modulate negative feedback to the hypothalamus and pituitary glands, supporting the production of testosterone at sustained, optimal levels.



## Alpha-Glycerophosphatidylcholine

Alpha-Glycerophosphatidylcholine (A-GPC) is a highly-absorbable form of choline that has been extensively researched for its benefits to neurological and cellular health. Choline, a water-soluble essential nutrient, is a primary building block of acetylcholine, a major neurotransmitter of the central nervous system. When low choline levels limit the synthesis of acetylcholine, peak physical and mental performance can be adversely affected. A-GPC also naturally increases secretion of hGH along with Growth Hormone Releasing Hormone.

Choline is the prime constituent of phospholipids (fatty acids), such as phosphatidyl choline (PC), which, as key components of cell membranes, are vital for healing and repair. The choline provided in the form of A-GPC serves as the precursor for the synthesis of PC from other lipid-based compounds.48-51 Recent studies show that choline improves balance and coordination when combined with 'skill set' practice and training. This is a result of normalized nerve transmission in the brain, and in cardiac, skeletal and smooth muscles.51-58

#### Lysine

The essential amino acids, L-arginine and L-lysine, exhibit a well-documented, synergistic relationship involved in several aspects of human physiology. In clinical studies, the combination of arginine and lysine increased nighttime levels of hGH more effectively than arginine alone. In one study neither one of these amino acids taken as single agents were able to raise growth hormone, only the combination of the two was effective.59

Arginine and lysine have also been shown to support bone metabolism and growth and to exert a positive effect on human osteoblasts. This is related partly to the production of factors required for matrix synthesis and partly to the direct or mediated activation of cell proliferation.<sup>60</sup>

### Chrysin

Chrysin belongs to a biologically active class known as bioflavonoids. Chrysin has been isolated from Passiflora plants, such as P. caerulea, used

as a sedative in folklore medicine<sup>61</sup> and *P. incarnata*, which is well-known in traditional medicine for its diverse biological effects.<sup>62</sup> Chrysin is also found in chrysanthemum flowers.

Chysin's aromatase-inhibiting ability has made it a popular supplement for bodybuilders and athletes to reduce estrogen conversion, thereby allowing more androgen to be produced and utilized.

Zinc

Zinc, a non-toxic, biologically-essential trace mineral, is vital for almost all physiological processes. Necessary to maintain the structural

integrity of DNA, zinc also plays a role in cellular metabolism, immune function, wound healing, and acts as a messenger in signal transduction. Zinc is vital for growth, reproduction, and reproductive health.63-70

Zinc is essential in the formation of hormone receptor proteins and for nuclear binding of androgen receptors. Zinc influences synthesis and secretion of hormones including LH (luteinizing hormone) and FSH (follicle-stimulating hormone). It is a key factor in gonadal differentiation, testicular growth, and many other aspects of male reproductive health. Hypogonadism is indicative of significant zinc deficiency in animals and humans.64,65,71,72

Zinc is an essential element in prostatic fluid and high amounts of zinc are secreted in the prostatic fluid. Zinc plays a key role in prostate health, influencing immunologicial, infectious, and neoplastic developments.73-75

Zinc is found to influence hormonal regulation of cell division. It does this through its influence on the pituitary growth hormone known as IGF-1, which is sensitive to zinc. When zinc is deficient, GH (growth hormone) can either increase or decrease, but circulating IGF-1 levels are seen to decrease consistently.76



Zinc is essential for the metabolism of melatonin which plays a key role in dopamine regulation. Zinc deficiency is found in many children diagnosed with ADHD and is being investigated for its possible benefits through its ability to support dopamine pathways.<sup>71,72</sup>

Zinc influences metabolism of nutrients and steroids in the liver. The livers of zinc deficient rats showed a higher aromatization of testosterone to estradiol than the control groups with significantly lower serum levels of testosterone, estradiol, and LH (leutenizing hormone).<sup>66</sup>

For more information on any of the ingredients listed here, including extensive research or individual monographs compiled by Donnie Yance, please email info@naturaedu. com.



# References

- Yeap BB, Hyde Z, Norman PE, et al. Associations of Total Testosterone, Sex Hormone-Binding Globulin, Calculated Free Testosterone, and Luteinizing Hormone with Prevalence of Abdominal Aortic Aneurysm in Older Men. J Clin Endocrinol Metab. 2010 Jan 8. [Epub ahead of print]
- Laughlin GA, Goodell V, Barrett-Connor E. Extremes of Endogenous Testosterone Are Associated with Increased Risk of Incident Coronary Events in Older Women. J Clin Endocrinol Metab. 2009 Nov 24. [Epub ahead of print] Department of Family and Preventive Medicine, School of Medicine, University of California, San Diego, La Jolla, California 92093.
- 3. European Heart Journal, June 2000; 21:868-894.
- 4. Golden SH, Maguire A, Ding J, et al. Amer. Journal of Epidemiology, 2002; 155(5): 437-445.
- Yeap BB, Chubb SA, Hyde Z, et al. Australia.byeap@cyllene.uwa. edu.au Lower serum testosterone is independently associated with insulin resistance in non-diabetic older men: the Health In Men Study. Eur J Endocrinol. 2009 Oct;161(4):591-8. Epub 2009 Aug 6. School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia 6009.
- 6. Bucci, Luke Ph.D. *Nutrients as Ergognenic Aids for Sports and Exercise*, Chapter 6, pg. 69, CRC Press, Boca Raton, 1993.
- 7. Koppeschaar HP, et al. Clin Endocrinol, vol. 36, no. 5, 1992 May.
- Rajfer J, Aronson WJ, Bush PA, et al. (1992) Nitric oxide as a mediator of relaxation of the corpus cavernosum in response to noadrenergic, noncholinergic neurotransmission. N England J Med 326: 90-94 Clin Invest, 97(5):1319-28, 1996, March.
- Cakir E, Ozcan O, Yaman H, et al. Z. Elevated plasma concentration of asymmetric dimethylarginine that is reduced by single dose testosterone administration in idiopathic hypogonadotropic hypogonadism patients. J Clin Endocrinol Metab. 2005 Mar; 90(3):1651-4. Epub 2004 Dec 21. Department of Emergency Medicine, Gulhane Military Medical School, 06010, Etlik, Ankara, Turkey. erdcakir@yahoo.com
- Boger RH, Ron ES L-Arginine improves vascular function by overcoming deleterious effects of ADMA a novel cardiovascular risk factor. 10(1):14-23 Mar. Altern Med Rev. 2005 Clinical Pharmacology Unit, Institute of Experimental and Clinical Pharmacology, Center of Experimental Medicine, University Hospital Hamburg-Eppendorf, Germany.
- 11. Hurson, M, et al. J. Paren and Enteral Nutr, 19 (3): 222-30, 1995, May-June.
- Polan, Mary Lake MD, PhD, MPH. J Womens Health Gend Based Med. 2001; 10(4):389-409, Stanford University School of Medicine in Stanford, California.
- Schwedhelm, E, Mass, R, Freese, R, Jung, D, et al. *Pharmacokinetic* and pharmacodynamics properties of oral L-citrulline and L-arginine: impact on nitric oxide metabolism. Br J Clin Pharmacol. 2008 January; 65(1): 51-59.
- Ochiai, M, Hayashi, T, Morita, et al. Short-term effects of L-citrulline supplementation on arterial stiffness in middle-aged men. Int J Cardiol (2010) doi:10,1016/j.ijcard.2010.10.0004
- 15. Leung AY, Foster S. *Encyclopedia of Common Natural Ingredients Used in Food, Drugs and Cosmetics.* 2nd ed. New York, NY: John



- Huang JH, Shen ZY, Chen WH. Exploration on molecular mechanism of epimediun flavonoids in regulating adrenocortical regeneration in rats with inhibited hypothalamic-pituitary-adrenal axis using oligonucleotide microarrays. Zhongguo Zhong Xi Yi Jie He Za Zhi. 2006 May;26(5):423-6. Chinese.
- Wu, T, Cui, L. Zhang, Z, et al. *Experimental study on antagonizing action of herba Epimedii on side effects induced by glucocorticoids*, Zhongguo Zhong Yao Za Zhi 21(12) 1996: 748-51, 763.
- Wang, YS. Pharmacology and applications of Chinese Materia Medica. p. 1102-81983
- Cai, WJ, Huang, JH, Zhang, SQ, et al. *Icariin and its derivative icariside II extend healthspan via insulin/IGF-1 pathway in C. elegans*. PLoS One 6(12) 2011: e28835.
- Yu, S, Chen, K and Li, S. *In vitro and in vivo studies of the effect of* a Chinese herb medicine on osteoclastic bone resorption. Chinese Journal of Dental Research 2(1) 1999: 7-11.
- Xue, L, Want, Y, Jiang, Y, et al. Comparative effects of er-xian decoction, Epimedium herbs, and icariin with estrogen on bone and reproductive tissue in ovariectomized rats. Evidence-Based Complementary and Alternative Medicine. Nov. 7, 2012, doi:10.1155/2012/241416.
- Wu, BY, Zou, JH and Meng, SC. Effect of wolfberry fruit and Epimedium on DNA synthesis of the aging-youth 2BS fusion cells. Zhongguo Zhong Xi Yi Jie He Za Zhi 23(12 2003: 926-28
- Chen, Kuang and Chen, Effect of monoamine neurotransmitters in the hypothalamus. Zhongguo Zhong Xi Yi Jie He Za Zhi 23(12 2003: 926-28
- Wang, YK and Huang, ZQ. Protective effects of icariin on human umbilical vein endothelial cell injury induced by H(2)O(2) in vitro. Pharmacological Research 52(2) 2005: 174-82.
- 25. Lubis, I., et al. *L-dihydroxyphenylalanine (I-dopa) in mucuna seeds.* Ann. Bogor. 1981; 7(3): 107–14.
- 26. Pruthi, Som C, et al. *Ayurvedic composition for the treatment of disorders of the nervous system including Parkinson's disease.* US patent #6,106,839. 2000.
- Liebert, Mary Ann. An alternative medicine treatment for Parkinson's disease: results of a multicenter clinical trial. HP-200 in parkinson's disease study group. J. Altern. Complement. Med. 1995; 1(3): 249–55.
- 28. Beal MF. *Bioenergetic approaches for neuroprotection in Parkinson's disease.* Ann Neurol. 2003;53 Suppl 3:S39-47; discussion S47-8.
- 29. Tripathi YB, Upadhyay AK. *Effect of the alcohol extract of the seeds of Mucuna pruriens on free radicals and oxidative stress in albino rats.* Biochemistry Section, Department of Medicinal Chemistry, Institute of Medical Sciences, Banaras Hindu University, Varanasi-221005, India.
- Guerranti, R, et al. Proteins from Mucuna pruriens and enzymes from Echis carinatus venom: characterization and cross-reactions. J. Biol. Chem. 2002; 277(19): 17072–28.
- 31. Bhargava, N C, et al. *Fortege, and indigenous drug in common sexual disorders in males.* Mediscope 1978; 21(6): 140–44.
- 32. Obreshkova, D, Pangarova, T, Milkov, S, et al. Comparative



Analytical Investigation of Tribulus terrestris Preparations. Publication in Pharmacia, vol. XLV, bk. 2/1998, 11. Sopharma Ltd. Summary: A comparative investigation in respect to qualitative and quantitative composition of raw materials from Tribulus t.

- Adimoelja A. Phytochemicals and the breakthrough of traditional herbs in the management of sexual dysfunctions. Int J Androl, 23 Suppl 2(): 82-4 2000.
- Tomowa, M, et al. Steroidal saponins from T. terrestris with a stimulating action on the sexual functions. Int. Conf. Chem. Biotechnol. Biol. Act. Nat. Prod. 3:298-302 (1981).
- 35. Zarkova S. Histological histochemical and histometric studies of the changes of spermatogenesis in laboratory and some domestic animals after treatment with the drug TB-68 Dissertation Thesis, 1977.
- Brown GA, Vukovich MD, Martini ER, et al. Effects of androstenedione-herbal supplementation on serum sex hormone concentrations in 30- to 59-year-old men. Int J Vitam Nutr Res. 2001 Sep; 71(5): 293-301. Exercise Biochemistry Laboratory, Department of Health and Human Performance, Iowa State University, Ames, IA.
- Seth SD, Jagadeesh G. Cardiac action of Tribulus terrestris. Indian J Med Res. 1976 Dec; 64(12): 1821-5. Indian J Physiol Pharmacol. 1971 Jul; 15(3): 93-6.
- Ang HH, Ikeda S, Gan EK. *Evaluation of the potency activity of aphrodisiac in Eurycoma longifolia Jack.* Phytother Res 2001 Aug; 15(5):435-6 School of Pharmaceutical Sciences, University Science Malaysia, Minden, 11800, Penang, Malaysia. (ISSN: 0951-418X)
- Ang HH. Effects of Eurycoma longifolia Jack (Tongkat Ali) on the initiation of sexual performance of inexperienced castrated male rats. Exp Anim 2000 Jan; 49(1):35-8 (ISSN: 1341-1357) Cheang HS; Yus of AP School of Pharmaceutical Sciences, University Science Malaysia, Penang, Malaysia.
- Ang HH, Cheang HS. Studies on the anxiolytic activity of Eurycoma longifolia Jack roots in mice. Jpn J Pharmacol 1999 Apr; 79(4):497-500 (ISSN: 0021-5198) School of Pharmaceutical Sciences, University Science Malaysia, Minden, Penang.
- Ang HH, Sim MK. *Eurycoma longifolia increases sexual motivation in sexually naive male rats*. Arch Pharm Res 1998 Dec;21(6):779-81 (ISSN: 0253-6269) School of Pharmaceutical Sciences, University of Science, Malaysia, Minden, Singapore.
- Ang HH, Sim MK. Eurycoma longifolia Jack and orientation activities in sexually experienced male rats. Biol Pharm Bull 1998 Feb; 21(2):153-5 (ISSN: 0918-6158) School of Pharmaceutical Sciences, University of Science Malaysia, Penang.
- Ang HH, Sim MK. Eurycoma longifolia Jack enhances libido in sexually experienced male rats. Exp Anim 1997 Oct; 46(4):287-90 (ISSN: 1341-1357) School of Pharmaceutical Sciences, University of Science Malaysia, Penang, Malaysia.
- Ang HH, Cheang HS. Effects of Eurycoma longifolia jack on laevator ani muscle in both uncastrated and testosterone-stimulated castrated intact male rats. Arch Pharm Res (Korea 2001 Oct; 24(5):437-40 (ISSN: 0253-6269) School of Pharmaceutical Sciences, University Science Malaysia, Minden, 11800, Penang, Malaysia.
- Ang HH, Ngai TH. Aphrodisiac evaluation in non-copulator male rats after chronic administration of Eurycoma longifolia Jack. Fundam Clin Pharmacol 2001 Aug;15(4):265-8 (ISSN: 0767-3981) School of Pharmaceutical Sciences, University of Science Malaysia, Minden, 11800, Penang, Malaysia.

- Tan S, Yuen KH, Chan KL. HPLC analysis of plasma 9-methoxycanthin-6-one from Eurycoma longifolia and its application in a bioavailability/pharmacokinetic study. Planta Med 2002 Apr; 68(4):355-8 (ISSN: 0032-0943) School of Pharmaceutical Sciences, University of Science Malaysia, Penang, Malaysia.
- Ang HH, Chan KL, Mak JW. Effect of 7-day daily replacement of culture medium containing Eurycoma longifolia Jack constituents on the Malaysian Plasmodium falciparum isolates. J Ethnopharmacol 1995 Dec 15; 49(3):171-5 (ISSN: 0378-8741) School of Pharmaceutical Sciences, University Science Malaysia, Penang.
- Parnetti L, et al. Multicentre study of I-alphaglycerylphosphorylcholine vs ST2000 among patients with probable senile dementia of Alzheimer's type. Drugs Aging 1993 Mar-Apr; 3,(2):159-64
- 49. Barbagallo Sanglorgi G, et al. *Alpha-glycerophosphocholine in the mental recovery of cerebral ischemic attacks. An Italian multicenter clinical trial.* Ann NY Acad Sci 1994 Jun 30; 717:253-69.
- Drago F, et al. Behavioral effects of I-alphaglycerlphosphosphorylcholine: influence on cognitive mechanisms in the rat. Pharmacol Biochem Behav 1992 Feb; 41(2):445-8.
- Lopez, CM, et al. Effect of a new cognition enhancer, alphaglycerlphosphorylcholine, on scopolamine-induced amnesia and brain acetylcholine. Pharmacol Biochem Behav 1991 Aug; 39(4):835-40.
- 52. Amemta F. Del Valle M, Vega JA, Zaccheo D. Age-related structural changes in the rat cerebella cortex: effect of choline alfoscarate treatment. Mech Aging Dev. 1991; 61: 173-186.
- 53. Amemta F, Ferrante F, Vega JA, Zaccheo D. Long term choline alfoscerate treatment counters age-dependent microanatomieal changes in rat brain. Prog Neuropsychopharmacol Biol Psychiatry. 1994; 18:915-924.
- 54. Ceda GP. Ceresini G. Denti L., et al, *Alpha-glycerylphorylcholine* administration increases the GH response to GHRH of young and eldery subjects. Horm Metab Res. 1992: 24:119-121.
- 55. Ricci A, Bronzenti E, Vega JA, Amenta F. Oral Choline alfoscerate counteracts age-dependent loss of mossy fibers in the rat hippocampus, Mech Aging Dev. 1992; 66: 81-91.
- Parnetti L, et al. Multicentre study of I-alphaglycerylphosphorylcholine vs ST2000 among patients with probable senile dementia of Alzheimer's type. Drugs Aging 1993 Mar-Apr; 3, (2):159-64.
- 57. Barbagallo Sanglorgi G, et al. *Alpha-glycerophosphocholine in the mental recovery of cerebral ischemic attacks. An Italian multicenter clinical trial.* Ann NY Acad Sci 1994 Jun 30; 717:253-69.
- Drago F, et al. Behavioral effects of I-alphaglycerlphosphosphorylcholine: influence on cognitive mechanisms in the rat. Pharmacol Biochem Behav 1992 Feb; 41(2):445-8.
- 59. Bazzarre, TL. Nutrition and strength, in Nutrition in Exercise and Sport. Wolinsky, I. (Ed.) CRC Press, Boca Raton, 1998, chap. 14.
- Torricelli P, Fini M, Giavaresi G, et al., L-Arginine and L-Lysine stimulation on cultured human osteoblasts.Biomed Pharmacother 2002;56:492-497.
- 61. Medina, JH, et al. (1998) Planta Med. (Dec).
- Tordera, M, et al., Influence of anti-inflammatory flavonoids on degranulation and arachidonic acid release in rat neutrophils. (1994) Z Nuturforsch ICI, 49 (3-4): 235-240.



- 63. Haase H, Rink L. *Multiple impacts of zinc on immune function*. Metallomics. 2014 Feb 17.
- 64. Gupta M, Mahajan VK, et al. *Zinc therapy in dermatology: a review*. Dermatol Res Pract. 2014. http://dx.doi.org/10.1155/2014/709152
- 65. ohn E, Laskow TC, et al. *Zinc in innate and adaptive tumor immunity*. J Translational Medicine. 2010. 8:118.
- 66. Om AS, Chung KW. *Dietary zinc deficiency alters 5a-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver*. J Nutr. 1996 January. 842-848.
- 67. Web: https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/
- Franklin RB, Costello LC. The important role of the apoptotic effects of zinc in the development of cancers. J Cell Biochem. 2009 April 1. 106(5):750-757.
- Alam S, Kelleher SL. Cellular mechanisms of zinc dysregulation: a perspective on zinc homeostasis as an etiological factor in the development and progression of breast cancer. Nutrients. 2012. 4:875-903. doi:10.3390/nu4080875
- 70. 8. Haase H, Rink L. *The immune system and the impact of zinc during aging*. Immunity & Aging. 2009. 6:9.
- 71. John E, Laskow TC, et al. *Zinc in innate and adaptive tumor immunity*. J Translational Medicine. 2010. 8:118.
- 72. Om AS, Chung KW. Dietary zinc deficiency alters 5a-reduction and aromatization of testosterone and androgen and estrogen receptors in rat liver. J Nutr. 1996 January. 842-848.
- 73. Web: https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/
- Franklin RB, Costello LC. The important role of the apoptotic effects of zinc in the development of cancers. J Cell Biochem. 2009 April 1. 106(5):750-757.
- Alam S, Kelleher SL. Cellular mechanisms of zinc dysregulation: a perspective on zinc homeostasis as an etiological factor in the development and progression of breast cancer. Nutrients. 2012. 4:875-903. doi:10.3390/nu4080875
- 76. 8. Haase H, Rink L. *The immune system and the impact of zinc during aging*. Immunity & Aging. 2009. 6:9.

