©Journal of Sports Science and Medicine (2008) **7,** 562-564
http://www.jssm.org

Letter to editor

Herbal supplements: cause for concern?

Dear Editor-in-chief

More than 1400 herbal products or herbal-derived compounds are commonly commercialised for health uses worldwide (Tyler, 1996). Herbs are considered dietary supplements, and therefore are subjected to a very limited form of regulation, and advertisements normally highlight their potential activities without mentioning any side effect. Also, herbs are generally believed to be 'natural', and hence safe. Many nutritional supplements contains herb compounds usually not present in the diet (e.g. Ginko biloba, horse-chestnut), and only 10% of the herbs used in nutritional supplements are commonly present in the food (e.g. garlic, soy, blueberry, green the, ginger, curcuma) (Eisenberg et al., 1993).

There is much interest in "alternative natural approaches" in sport. It is appealing for athletes to use 'natural' substances with similar activity to 'pharmacological' ones in term of improving performance, are not considered doping, and are considered side-effects free (Table 1). Indeed, many herbal dietary supplements marketed on internet are presented as legal alternative to illicit drugs (Denneey et al., 2005).

Ecdysteroids

Ecdysteroids are the steroid hormones of arthropods (Figure 1). They also occur in some plants, where they are known as phytoecdysteroids, and are believed to contribute to deter invertebrate predators. In insects, they regulate moulting and metamorphosis, may regulate reproduction and diapause. Most actions of ecdysteroids are mediated by intracellular receptor complexes, which regulate gene expression in a tissue- and development-specific manner (Lehmann et al 1989).

Several phytoecdysteroids have anabolic growth-promoting effects on mice, rats, pigs and Japanese quails. Ecdysteroids stimulate muscle growth, and this anabolic effect promotes increased physical performance without training. Ecdysteroids are also able to increase muscle ATP content in vitamin D-deprived rats (Báthori, 2002).

Ecdysteroids stimulate protein synthesis in the mouse liver, heart and muscles, and act on lipids methabolism, reduce glucagon-induced hyperglycaemia, and enhance glucose utilization by tissues. The mechanism involved seems to be an increase of tissue sensitivity to insulin (Bathori and Pongracz, 2005).

Phytooestrogens

Phytooestrogens are biologically active plant substances with a chemical structure similar to oestradiol. This structural similarity accounts for their ability to bind to oestrogen receptors, and exert various oestrogenic or anti-oestrogenic effects. There are three main classes of phytooestrogens: isoflavones, coumestans, and lignans. Most of the phytooestrogens have a higher affinity to oestrogen receptor beta than alpha. The former is strongly expressed in the ovary, uterus, brain, bladder, testis, prostate, bone, cardiovascular system, and lungs. Expression of oestrogen receptor beta appears to occur at different sites in the brain than oestrogen receptor alpha. (Setchell and Cassidy, 1999)

The oestrogenic effect of phytooestrogens produces reproductive disturbances in sheep, and a phytooestrogen-rich diet is associated with a lower risk of breast and prostate cancer, and of cardiovascular disease (Adlercreutz, 1990). *In vitro*, phytooestrogens exert both proliferative (oestrogenic) and antiproliferative (antioestrogenic) effects in human cell lines (Wang et al., 1996). In humans, isoflavones increase the length of the follicular phase, with suppression of the midcycle surges of FSH and LH. Some dietary phytooestrogens can produce mild oestrogenic effects in postmenopausal women, including

Table 1. Summary of herbs derived products and their proven or advertised activity.

PLANT/HERB	SUBSTANCE	DESCRIBED/PROVEN ACTIVITY
Ajuga Turkestanica	Turkesteron	Anabolic
Raphonticum Carthamoides	Ecdysterone Ponasteron A	Anabolic
Cyanotis Vaga	Commisteron	Anabolic
Bacopa Monnieri	Ecdysterone	Anabolic
Commiphora Mukul	Guggulsteron	Activate alpha isoform of estrogen receptor, increase fibrinolytic activity, reduce platelets aggregation
Gotu Kola	Fucosterol Stigmasterol B-sistosterol Campesterol	Anabolic and anti-hystaminergic
Smilax officinalis	Fucosterol Stigmasterol B-sistosterol Campesterol	Anabolic and anti-hystaminergic
Muira Puama	Fucosterol Stigmasterol B-sistosterol Campesterol	Anabolic and anti-hystaminergic
Tribulus Terrestris	Protodioscin	A supposed but not proven increase in LH
Eurycoma Longifolia	Methoxyflafon	Competitive inhibitor of p450 Inhibition of CYP19
Vitex Agnus Castus	Flavonoids	Oestrogenic
Astragalus Root	Flavonoids	Oestrogenic

Received: 26 October 2008 / Accepted: 28 October 2008 / Published (online): 01 December 2008

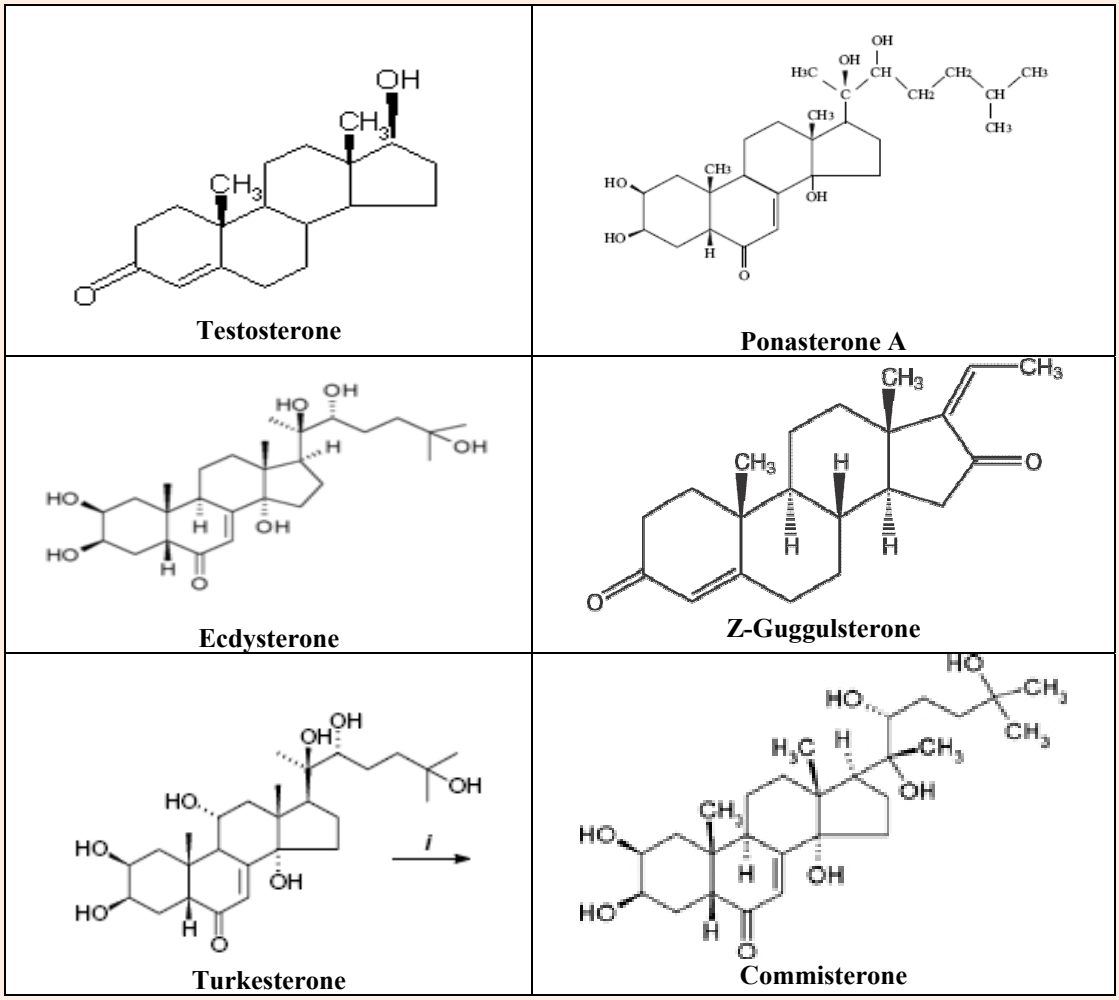

Figure 1. Chemical structure of the most commonly advertised herb-derived molecules.

oestrogen-like effects on vaginal cytology and reductions in hot flushes, and oestrogen-like activity on bone and lipid metabolism (Cassidy et al., 1994). Isoflavones demonstrate anticarcinogenetic activity, inhibiting angiogenesis and cell progression, inhibiting aromatase enzyme, and stimulating sex hormone binding globulin synthesis (Messina et al., 2006).

Most of the phytooestrogens-based preparations freely available on the market are proposed as legal and non-toxic anti-oestrogenic compounds (to counterbalance the side effects of anabolic steroids, mainly based on methoxyflafones (Usui, 2006)), as fat lowering products or sexual enhancing compounds based mainly on plant extracts from Commiphora Mukul (Guggulsterone), Eurycoma Longifolia (methoxyflavone), Vitex Agnus Castus and Astragalus Root (isoflavones).

Plant sterols

Plant sterols interfere with the uptake of both dietary and biliary cholesterol from the intestinal tract in humans. They appear to decrease the solubility of cholesterol in the oil and micellar phases, thus displacing cholesterol from bile salt micelles and interfering with its absorption.

Fish develop infertility when exposed to high levels of wood pulp, which is rich in sitosterol, in the water. High levels of intake of plant sterols may produce an oestrogenic effect, with a significant decrease in testicular weight and sperm concentrations after beta-sitosterol treatment. An increase in the uterine weight of female rats and an increase in basal luteinizing hormone secretion in immature male and female rabbits were also observed following plant sterols treatment.

The clinical significance of these findings in humans is unknown, as studies in mammals did not demonstrate any oestrogenic effect *in vivo* or *in vitro* (Baker et al., 1999). Plant sterols do not bind to oestrogen receptors. Furthermore, plant sterols do not stimulate transcriptional activity of human oestrogen receptors (Baker et al., 1999).

A large number of plant sterols-based preparations are freely available on the market. Most of them are proposed as legal and non-toxic anabolic and fat lowering products, and as sexual enhancing compounds based mainly on plant extracts coming from Gotu Kola, Smilax Officinalis, Muira Puama (which contain fucosterol, stigmasterol, sistosterol, and campesterol).

An overview

Some herbal products may be safe and may contain active constituents with beneficial physiologic effects. Also, some herbs are safe in modest amounts but they may become toxic at higher doses. For example, liquorice root can be used safely for treating duodenal and gastric ulcers,

but large amounts of liquorice can cause serious side effects such as hypokalemia, high blood pressure, and heart failure. Finally, other herbs, toxic by themselves: for example, germander, an herb used in some weight-loss programs, can cause fatal hepatitis. Other herbs may be toxic because of possible contaminants: the Chinese herbs caowu and chuanwu used for the management of rheumatism, arthritis, bruises, and fractures may contain highly toxic potentially fatal alkaloids such as aconitine.

Therefore, despite the increased tendency to seek natural therapies, athletes have to be aware that "natural" does not equal to "safe." Herbs should not be touted as miraculous side effects-free substances, but rather as compounds that work through simple biochemistry. The effects of most herbal supplements have not been studied using rigorous scientific methodology, and the hyperbolic advertising and advocacy literature surrounding herbal products often contains untested claims, and under-reports side effects.

All the preparations mentioned above exhibit hormone-like activity. Evidence in animals of reproductive disturbances associated with ingestion of feed rich in oestrogenic substances includes a lower conception rate in sheep after prolonged isoflavones consumption, infertility in cattle after consuming feed containing coumestrol, decreased fertility in captive cheetahs fed with dietary oestrogens, hyperoestrogenism in pigs fed with diets containing zearalenone, uterotropic effects in mice fed with soybean, reduced fecundity in adult males rats fed a high phytoestrogen diet for 3 days (Glover and Assinder 2006; Srilatha, 2004) Also, in a population-based cohort study in the United Kingdom, a vegetarian diet during pregnancy was associated with a 5-fold higher risk of hypospadias, and consumption of a high phytooestrogens containing diet can prolong the follicular phase of the menstrual cycle by suppressing FSH and LH secretion. Unfortunately, little it is known about the endocrinological and reproductive side effects of the mentioned herbal preparations, and even less is known when considering that the used dosages for increasing physical performances have not been studied at all. Given the risks of both short and long term toxicity, side effects and drug interaction, studies regarding the use of herbal supplements are essential (Glover and Assinder, 2006). Athletes should be aware that the safety of these supplements is still unproven, their effect as performance enhancers has not been shown, and the long term effects are unknown.

Paolo Borrione[1], Luigi Di Luigi [1], Nicola Maffulli [2]✉ and Fabio Pigozzi [1]

[1] Department of Health Sciences - University of Rome "Foro Italico" Italy. [2] Department of Trauma and Orthopaedic Surgery, Keele University School of Medicine, Hartshill, UK

References

Adlercreutz, H. (1990) Western diet and western diseases: some hormonal and biochemical mechanisms and associations. *Scandinavian Journal of Clinical and Laboratory Investigation* **201,** 3-23.

Baker, V.A., Hepburn, P.A., Kennedy, S.J., Jones, P.A., Lea, L.J., Sumpter, J.P. and Ashby, J. (1999) Safety evaluation of phytosterol esters. Part 1. Assessment of estrogenicity using a combination of in vivo and in vitro assays. *Food and Chemical Toxicology* **37,** 13-22.

Bathori, M. (2002) Phytoecdysteroids effects on mammalians, isolation and analysis. *Mini Reviews in Medicinal Chemistry* **2,** 285-293.

Bathori, M. and Pongracz, Z. (2005) Phytoecdysteroids-from isolation to their effects on humans. *Current Medicinal Chemistry* **12,** 153-172.

Cassidy, A., Bingham, S. and Setchell, K.D.R. (1994) Biological effects of a diet of soy protein rich in isoflavones on the menstrual cycle of premenopausal women. *The American Journal of Clinical Nutrition* **60,** 333-340.

Denneey, C.E., Tsourounis, C. and Miller, A.E. (2005) Evaluation of herbal dietary supplements marketed on the internet for recreational use. *The Annals of Pharmacotherapy* **39,** 1634-1639.

Eisenberg, D.M., Kessler, R.C., Foster, C., Norlock, F.E., Calkins, D.R. and Delbanco, T.L. (1993) Unconventional medicine in the United States: prevalence, costs, and patterns of use. *The New England Journal of Medicine* **328,** 246-252.

Glover, A. and Assinder, S.J. (2006) Acute exposure of adult male rats to dietary phytoestrogens reduces fecundity and alters epididymal steroid hormone receptor expression. *The Journal of Endocrinology* **189,** 565-573.

Lehman, M. and Koolman, J. (1989) Ecdysteroid receptors of the blowfly Calliphora vicina. Characterization of binding to nonspecific DNA. *European Journal of Biochemistry* **181,** 577-582.

Messina, M., McCaskill-Stevens, W. and Lampe, J.W. (2006) Addressing the soy and breast cancer relationship: review, commentary, and workshop proceedings. *Journal of the National Cancer Institute* **98,** 275-284.

Setchell, K.D. and Cassidy, A. (1999) Dietary Isoflavones: Biological Effects and Relevance to Human Health. *The Journal of Nutrition* **129,** 758-758.

Srilatha, B. and Adaikan, P.G. (2004) Estrogen and phytoestrogen predispose to erectile dysfunction: do ER-alpha and ER-beta in the cavernosum play a role? *Urology* **63,** 382-386.

Tyler, V.E. (1996) What pharmacists should know about herbal remedies. *Journal of the American Pharmaceutical Association* **NS36,** 29-37

Usui, T. (2006) Pharmaceutical prospects of phytoestrogens. *Endocrine Journal* **53,** 7-20.

Wang, T.T.Y, Sathyamoorthy, N. and Phang, J.M. (1996) Molecular effects of genistein on estrogen receptor mediated pathways. *Carcinogenesis* **17,** 271-275.

✉ **Nicola Maffulli,**
Department of Trauma and Orthopaedic Surgery, Keele University Medical School, Store On Trent, England.
E-mail: n.maffulli@keele.ac.uk