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 (Dennecey 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 metabolism, 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.

<table>
<thead>
<tr>
<th>PLANT/HERB</th>
<th>SUBSTANCE</th>
<th>DESCRIBED/PROVEN ACTIVITY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajuga Turkestanica</td>
<td>Turkesteron</td>
<td>Anabolic</td>
</tr>
<tr>
<td>Raphonticum Carthamoides</td>
<td>Ecdysterone</td>
<td>Anabolic</td>
</tr>
<tr>
<td>Ponasteron A</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyanotis Vaga</td>
<td>Commisteron</td>
<td>Anabolic</td>
</tr>
<tr>
<td>Bacopa Monnieri</td>
<td>Ecdysterone</td>
<td>Anabolic</td>
</tr>
<tr>
<td>Commiphora Mukul</td>
<td>Guggulsteron</td>
<td>Activate alpha isoform of estrogen receptor, increase fibrinolytic activity, reduce platelets aggregation</td>
</tr>
<tr>
<td>Gotu Kola</td>
<td>Fucosterol Stigmasterol</td>
<td>Anabolic and anti-hystaminergic</td>
</tr>
<tr>
<td></td>
<td>B-sistosterol Campesterol</td>
<td></td>
</tr>
<tr>
<td>Smilax officinalis</td>
<td>Fucosterol Stigmasterol</td>
<td>Anabolic and anti-hystaminergic</td>
</tr>
<tr>
<td></td>
<td>B-sistosterol Campesterol</td>
<td></td>
</tr>
<tr>
<td>Muira Puama</td>
<td>Fucosterol Stigmasterol</td>
<td>Anabolic and anti-hystaminergic</td>
</tr>
<tr>
<td></td>
<td>B-sistosterol Campesterol</td>
<td></td>
</tr>
<tr>
<td>Tribulus Terrestris</td>
<td>Protodioscin</td>
<td>A supposed but not proven increase in LH</td>
</tr>
<tr>
<td>Eurycoma Longifolia</td>
<td>Methoxyflafon</td>
<td>Competitive inhibitor of p450 Inhibition of CYP19</td>
</tr>
<tr>
<td>Vitex Agnus Castus</td>
<td>Flavonoids</td>
<td>Oestrogenic</td>
</tr>
<tr>
<td>Astragalus Root</td>
<td>Flavonoids</td>
<td>Oestrogenic</td>
</tr>
</tbody>
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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 methoxyflavones (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, sitosterol, 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 cattle after consuming feed containing coumestrol, sheep after prolonged isoflavones consumption, infertility and Fabio Pigozzi 1

in the United Kingdom, a vegetarian diet during pregnancy was associated with a 5-fold higher risk of hypothyroidism, arthritis, bruises, and fractures may contain highly toxic potentially fatal alkaloids such as aconitine.

References

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