

# Herbal Medicines: Are they really safe?

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### Introduction

Herbal medicines are widely available over the counter from many outlets such as health food shops, pharmacists or easily obtained over the internet. In a world now obsessed with organic and natural products, herbal medicines are becoming popular. Despite the unprecedented range of therapeutic drugs available, demand for herbal remedies is steadily increasing<sup>1</sup>. A simple search on the internet reveals many products available to help a variety of ailments. Many accredit their products as being "100% natural – no side effects" or "a safe alternative to prescription drugs". Even more concerning is the number of patients who believe a combination of their regular prescription drugs and complementary therapies can only be beneficial. The volume of literature available has increased over the last few years, with books on herbal medicines and other alternative medicines being widely available.

Due to an increase in literature, doctors are becoming more aware of herbal medicine use. However, patients are often not forth coming with their own self-dosing as they do not realise the potential for serious adverse reactions with what they believe is a natural product.



Over the past few years, a number of alternative medicines sold over the internet as being 100% natural have been found to contain synthetic, prescription or illegal drugs. The Food and Drug Administration (FDA) and the Medicines and Healthcare products Regulatory Agency (MHRA) have issued several advisory warnings concerning certain products available in the UK and internationally. This poster gives examples of herbal remedies found or thought to contain prescription or illegal drugs. Included is a more detailed example of a recent case received at this laboratory.

### Herbal remedies and the law

Products that claim to contain ingredients of natural or 'botanical' origin, until recently, were not subject to the same licensing laws as other prescription drugs. Herbal products lie in a 'grey area' between medicines and food products and provided the product did not make any reference to medicinal claims, the products were not subject to the same legislation as medicines. The majority of herbal products in the UK were marketed without medical claims and were therefore controlled under food legislation<sup>1</sup>. Currently there are two categories of herbal medicines; licensed and unlicensed. The majority of herbal medicines have been available for some time and once held Product Licences of Right (PLR). Since the implementation of EC legislation in 1995, all new licensed herbal products were assessed prior to marketing by the MHRA for safety, efficacy and quality. However, there were still many unlicensed herbal products on the market which, under legislation until recently, did not have to meet standards in quality or safety. Specific EC guidelines did exist on 'Quality of Herbal Remedies' and 'Manufacture of Herbal Medicinal Products'<sup>1</sup> but these remained simply guidelines.

It was suggested that the laws or their wording be altered so that specific licensing controlled all herbal medicine products. This was further endorsed by the increasing number of products now being discovered to contain unstated ingredients or even illegal drugs to increase their effects. Although the MHRA could remove such products from sale, the frequency of products being withdrawn could be reduced by monitoring the release of herbal products in the first place.

A new **European Directive on Traditional Herbal Medicinal Products** was implemented in the EU on 31 March 2004. It introduced registration for all herbal medicinal products with member states having to take necessary measures to comply by 30 October 2005. The Directive describes how applicants must submit a dossier relating to tests and trials carried out on the product. Clinical trials may not be necessary if the "efficacy of the product is plausible on the basis of long standing use and experience"<sup>2</sup>, referring to traditional medicines. However, most importantly, "a long tradition does not exclude the possibility that there may be concerns over the products safety"<sup>2</sup>. On 30<sup>th</sup> October 2005 UK Statutory Instruments No. 2791 and 2750 were published. The former describes the formation of **The Herbal Medicines Advisory Committee Order**, the latter, **The Medicines (Traditional Herbal Medicinal Products for Human Use) Regulations 2005**. Both these Instruments bring into force regulations set out in the European Directive above.

### Chinese medicines

Chinese herbal medicines are available throughout the UK and are thought to be worth £54 million in 1999<sup>3</sup>. Some Chinese medicines have been found to contain unknown and potentially dangerous toxins. Chinese 'Love Stones' seen by the Forensic Science Service<sup>4</sup> and found in analysis of amnesty bin contents at this laboratory<sup>5</sup>, contain the class A compound Bufotenine, found in toad secretions. The MHRA has issued advice to consumers specifically concerning the poor quality of some traditional Chinese medicines found in the UK. It advises specifically to avoid products not labelled in English<sup>6</sup>.



www.store.orientalpharmacy.com/nubaofook.html

The Chinese traditional medicine **Shubao Slimming Capsules** was suspected to have caused a case of irreversible liver failure in 2004 in the UK, requiring a liver transplant. It is believed the product claimed to contain botanical ingredients, but is suspected to have illegally contained undeclared **nitrosufenfluramine**, known to be hepatotoxic. This compound is closely related to the prescription only medicine fenfluramine.<sup>6</sup>

Slimming aid **Qing zhiisan tain shou** is on sale in the UK in the form of a cream and capsules. It has been found to contain the prescription only medicine sibutramine. **Sibutramine** can cause a rise in blood pressure and should only be prescribed under specific circumstances.<sup>6</sup>

### Anti-impotence herbal remedies

Drugs to treat impotence are widely available and extremely popular. Due to the nature of the problem help is often sought in private, with the internet and mail order offering an easy and confidential solution. Also, the conventional drug used in the treatment of impotence, sildenafil, can cause undesirable side effects and is potentially life-threatening if taken in conjunction with other prescription drugs e.g. nitrate-based drugs used in angina. As a result men and women turn to natural remedies as an alternative.

**Satibo** is one of many herbal products available on the internet that claim to be "all natural Chinese herbal formula" and "100% natural ingredients" as an alternative to Viagra<sup>®</sup>. As with Satibo, these products often claim that they bear non of the side effects many consumers experience with pharmaceutical anti-impotence medicines. Satibo makes many claims on its website for improving sexual experiences. It is not known whether this product contains any synthetic drugs.



www.satibo-online.co.uk

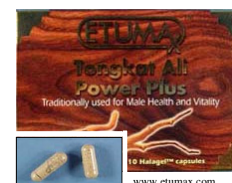
**Vinarol** (Virilex), however, is another product sold as a substitute to Viagra<sup>®</sup> that was found to be adulterated with sildenafil, the active drug in Viagra<sup>®</sup>. The FDA issued a recall notice for the product in 2003 due to "...serious adverse health consequences or death"<sup>7</sup>. The reason for the seriousness of the recall notice is due to the potential harm that sildenafil can cause to patients who are taking other kinds of medication. Men with erectile dysfunction can often have other associated medical problems such as diabetes, heart disease or hypertension. Sildenafil produces a life-threatening rise in blood pressure in such patients and more specifically if taken with nitrate based drugs often prescribed for chest pain. If a man is advised against sildenafil and turns to a herbal alternative such as Vinarol, he is facing the same set of risks that he was trying to avoid.<sup>7</sup>



www.nature-tone.com/sexual\_enhancement.html

**Hua Fo tablets**, a chinese herbal preparation imported since 1999, was recalled by Health Canada in 2002 as they were found to contain a drug similar to sildenafil.<sup>8</sup> The product was sold over the counter in approved and unapproved forms, but did not undergo any pre-market testing. After complaints that it was being marketed inappropriately, it was tested and found to contain an erectile-dysfunction drug similar to sildenafil.

### Case Study: Tongkat Ali



www.etumax.com

**Tongkat Ali Power Plus** capsules in original packaging were received at this laboratory for analysis from a GP in the London area. A 50 year old male patient on  $\alpha$  and  $\beta$  adrenoreceptor blocking agents, who took a proprietary brand of sildenafil weekly, was introduced to Etumax<sup>®</sup> by a friend. The patient reported a "generous improvement in his sexual libido and ability" and raised suspicions with his GP concerning the content and safety of this herbal medicine. The

patient was reassured by the Etumax<sup>®</sup> website<sup>9</sup> that states "100% natural herbal formulation", with approval from the Malaysian Ministry of Health, as well as compliance with GLP and GMP. The website goes on to say that Etumax<sup>®</sup> is a result of careful quality control with the absence of side effects and no contraindications, providing freedom specifically from sildenafil and heavy metals.

### References:

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- Kenyon et al Analysis for Identification in Amnesty Bin Samples from Dance Venues. *Ther Drug Monit.* 2005 Dec;27(6):793-798

Tongkat Ali capsules were analysed by gas chromatography with mass spectrometry (GC-MS), liquid chromatography with tandem mass spectrometry (LC-MS-MS), ultra violet spectrophotometry (UV) and thin layer chromatography (TLC). Secondary analysis was also completed at a separate laboratory.

The capsules were **positive for sildenafil** by GC-MS, LC-MS-MS, UV and TLC. Preliminary quantitations show approximately 20mg sildenafil per capsule. Capsules were **positive for tadalafil** by LC-MS-MS. Further analysis, with quantitations for both these drugs continues.

### Tadalafil



**Tadalafil (Cialis®)** is another drug used for erectile dysfunction. Like sildenafil, tadalafil is a prescription only medicine, but is easily available over the internet. It is a more potent anti-impotence drug with pharmaceutical effects occurring quicker and lasting up to 36 hours (24 hours longer than Viagra<sup>®</sup>). However, dose should not exceed 20mg a day and daily use is not recommended. It is contraindicated in patients with cardiac disease, angina, arrhythmias, hypotension and previous heart attacks.<sup>10</sup>



Cialis® is a copyright of Lilly

**Secondary analysis** by another laboratory showed the presence of the Tadalafil by GC-MS and LC-ESI-MS-MS. ICP-MS showed presence of **arsenic and lead**, along with other toxic metals. Microbiological tests were negative. The report concluded that due to these findings, the capsules were **not suitable for human consumption**.

### Conclusions

- Although new legislation has been put in place very recently to try to bring herbal medicines under control, members of the public and physicians should remain aware of the potential of unstated drugs in such products.
- Physicians should be aware that serious adverse reactions may occur in patients combining conventional and complementary therapies.
- Patients may not raise any suspicions to products that claim to be 'natural'.
- Patients should consult their GP's or pharmacists when thinking of turning to herbal alternatives to treat symptoms or supplement other treatment.

<sup>6</sup> Medicines and Healthcare products Regulatory Agency website 2005 www.mhra.gov.uk

<sup>7</sup> Mitka M. FDA issues warning on "all-natural" herbal product found to contain Viagra. *JAMA*, June 4, 2003 vol 289, no. 21

<sup>8</sup> Woolerton, E. Hua Fo tablets tainted with sildenafil-like compound. *JAMC* 2002 166(12)

<sup>9</sup> www.etumax.com

<sup>10</sup> Monthly Index of Medical Specialities. Haymarket Medical Publications Ltd. Dec 2004

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