

# Potential Risks Associated with the Use of Herbal Anti-Obesity Products

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## Abstract

The public wants an easy way to control obesity. Herbal anti-obesity products attract users because of their health claims, assumed safety, easy availability and extensive marketing. These products can be very heterogeneous in nature and have unpredictable levels of active ingredients, and unpredictable and potentially harmful effects. They may contain highly toxic herbs (e.g. *Aristolochia* species), potent herbs not recommended for use in weight control (e.g. *Ephedra sinica*) and herbal laxatives with potential hepatotoxic and nephrotoxic effects (e.g. anthraquinones). However, the presence of such herbs may not be disclosed on the product label. They may contain adulterants (e.g. drugs, drug analogues and thyroid extracts), including drugs that have been withdrawn from the market (e.g. fenfluramine). For all these reasons, herbal anti-obesity products can cause direct toxicity or adverse interactions with concurrent medications. Physicians and other healthcare professionals need to be aware of the problem. They should warn their patients about the heterogeneous nature of these agents and the potential risks associated with their use. They should report suspected adverse reactions to their national spontaneous reporting system.

Obesity is now an epidemic with an increasing prevalence in most parts of the world.<sup>[1]</sup> Diet and exercise are the mainstay of management of obesity, but the public wants an easy way to control obesity. Herbal anti-obesity products attract users because of their health claims, assumed safety, easy availability and extensive marketing.<sup>[2,3]</sup> There is no perceived need for professional assistance. Use of these products may also represent an alternative to failed attempts at weight control with more conventional approaches.<sup>[4]</sup> However, because of the known and emerging safety issues,<sup>[5–7]</sup> herbal anti-

obesity products are not recommended as part of a weight loss programme.

## 1. Potential Risks Associated with the Use of Herbal Anti-Obesity Products

Herbal anti-obesity products, including those available from shops and the internet, can be very heterogeneous in nature. They have unpredictable levels of active ingredients, and unpredictable and potentially harmful effects.<sup>[8]</sup>

Adverse effects of these products can be attributed to the intrinsic toxicity of the herbs,

herb-drug interactions and adulterants (conventional drugs), including drugs that have been withdrawn from the market.

## 2. Intrinsic Toxicity of Herbs

Several *Aristolochia* species have been used in traditional medicine in many parts of the world.<sup>[9]</sup> However, their use is no longer permitted in many countries due to toxicity of the aristolochic acid constituents, which are potent nephrotoxins and carcinogens.<sup>[9,10]</sup> Because of erroneous substitution and misidentification due to similar appearance, or confusion about the nomenclature,<sup>[11]</sup> herbal anti-obesity agents may contain *Aristolochia* species (*A. fangchi*) instead of the intended, non-toxic herb, *Stephania tetrandra*.<sup>[12]</sup> Inappropriate and prolonged use of *Aristolochia* species can result in aristolochic acid nephropathy, a rapidly progressive interstitial nephritis and urothelial malignancy due to aristolochic acid exposure.<sup>[10]</sup> Several factors may determine the risk among users, including duration of use, accumulated dose, differences in cytochrome P450 enzymes involved in the bioactivation and detoxification of aristolochic acid, and concurrent use of other phytotoxins.<sup>[10,13]</sup> Herbal products containing *A. fangchi* or *A. manshuriensis* may still be sold on the web or the market as treatment for obesity and other conditions despite worldwide publicity of nephrotoxic effects.<sup>[14-16]</sup> Herbal products allegedly containing *S. tetrandra* may test positive for aristolochic acid,<sup>[14,16]</sup> suggesting that substitution by *Aristolochia* species still occurs and such products may contain different herbs from those indicated on the label.

Herbal anti-obesity products may contain potent herbs not intended for use in weight control. For example, dietary supplements containing ephedra alkaloids and guarana-derived caffeine have been widely promoted for purposes of weight reduction and energy enhancement.<sup>[17]</sup> Ephedrine and related alkaloids have  $\alpha$ - and  $\beta$ -adrenergic receptor agonist activity. Their misuse or abuse may result in severe hypertension, palpitations, tachycardia, myocardial infarction, stroke, seizure, psychiatric disorders

and death.<sup>[17,18]</sup> The cardiovascular and CNS effects of ephedrine are potentiated by other stimulants such as caffeine.<sup>[17]</sup>

Herbal anti-obesity products may contain anthranoid laxatives.<sup>[19-21]</sup> The anthranoids (anthraquinones, anthrones and dianthrones) are peristaltic stimulant laxatives.<sup>[22]</sup> In some detoxifying and slimming products,<sup>[23]</sup> anthraquinone-containing herbs may be present, including senna (*Cassia senna* or *Cassia angustifolia*), cassia (*Cassia obtusifolia*), cascara sagrada (*Rhamnus purshiana*), rhubarb (*Rhamnus palmatum*), Chinese cornbind (*Polygonum multiflorum*) and aloe (*Aloe vera*). However, the presence of such herbs may not be disclosed on the product label. Also missing in many products is a warning statement. Some studies have revealed a risk for colorectal cancer associated with the use of anthraquinone-containing laxatives, but other studies have not.<sup>[22]</sup> Because of the possibility of a carcinogenic risk, chronic or long-term use cannot be recommended.<sup>[22,24]</sup> For the above reasons, and because of their potential hepatotoxic and nephrotoxic effects,<sup>[19-21]</sup> such herbal remedies should be used under medical supervision.

## 3. Herb-Drug Interactions

Toxic effects can be due to adverse interactions between herbal anti-obesity products and drugs. Ephedrine can produce a sympathomimetic toxidrome marked by hypertension, tachycardia, mydriasis, diaphoresis, hyperthermia, agitation and hallucination, especially in overdose and in the presence of other sympathomimetic agents.<sup>[17,18,25]</sup>

Chronic use and overdose of anthraquinones can lead to abdominal pain, diarrhoea, and fluid and electrolyte depletion.<sup>[22,24]</sup> Dehydration and direct nephrotoxicity increase the risk of renal failure during concurrent use of NSAIDs.<sup>[19,20]</sup> Due to the increased risk of hypokalaemia, patients taking diuretics, corticosteroids or liquorice should avoid taking anthranoid laxatives concomitantly.<sup>[24]</sup> Hypokalaemia, if present, increases the risk of toxicity in patients taking cardiac glycosides, antiarrhythmic drugs (arrhythmogenic

effects) and drugs inducing QT-prolongation (which predisposes to torsade de pointes).<sup>[24,26,27]</sup>

Prolonged intake of anthraquinones can cause hepatic damage, especially in the presence of other hepatotoxic agents.<sup>[19,21]</sup>

#### 4. Adulterants

Problems can also occur if herbal anti-obesity products contain adulterants (e.g. drugs, drug analogues and thyroid extracts), with the potential to cause direct toxicity, adverse drug-drug and drug-herb interactions.<sup>[8]</sup>

Adulterants commonly identified in proprietary anti-obesity products include appetite suppressants such as sibutramine.<sup>[8,28]</sup> Sibutramine is licensed for short-term use in obesity under strict medical supervision.

Other laxatives (e.g. bisacodyl) and drugs to mask the adverse effects of adulterants (e.g. propranolol) may also be found.<sup>[8,28]</sup>

Most important of all, adulterants that have long been banned because of their toxicity may also be found.<sup>[8,28-30]</sup> Phenolphthalein, an over-the-counter laxative, has been removed from the market because of concerns over carcinogenicity.<sup>[31]</sup> Fenfluramine was withdrawn from the market in 1997 because of the risk of valvular heart disease and pulmonary hypertension.<sup>[30]</sup> As herbal products can be poorly standardized, inadvertent overdose of adulterants may occur. One patient developed severe fenfluramine toxicity 2 hours after her first dose of a herbal anti-obesity agent.<sup>[30]</sup>

N-nitroso-fenfluramine is a derivative of fenfluramine. Neither pharmacological nor toxicological studies have been reported for this drug analogue. From 2001 to the summer of 2002, over 800 cases of liver damage were reported in Japan among subjects using herbal anti-obesity products containing N-nitroso-fenfluramine.<sup>[32]</sup> This fenfluramine derivative might have been added to enhance the weight loss effect or mask the presence of fenfluramine.<sup>[33]</sup> In Hong Kong, a 33-year-old hepatitis B virus carrier developed fulminant liver failure necessitating liver transplantation after taking a proprietary anti-obesity agent containing anthraquinones and the highly hepatotoxic N-nitroso-fenfluramine.<sup>[21]</sup>

There are several reports of thyrotoxicosis caused by herbal anti-obesity products that are adulterated with thyroid hormones or animal thyroid tissues.<sup>[34,35]</sup> Some products also contain caffeine and sibutramine, which can aggravate the symptoms of thyrotoxicosis.<sup>[35]</sup> In France, an anti-obesity product adulterated with pig thyroid glands caused several serious cases of thyrotoxicosis requiring intensive care unit admission.<sup>[36]</sup>

#### 5. Educational Messages

Herbal anti-obesity products are not recommended as part of a weight loss programme, since they have unpredictable amounts of active ingredients, and unpredictable and potentially harmful effects.

Physicians and other healthcare professionals need to be aware of the problem. They should warn their patients about the heterogeneous nature of these products and the potential risks associated with their use. It is important to recognize that herbal products are not required to undergo the same quality control and safety testing as prescription and over-the-counter medicines. These medicines are strictly regulated, but herbal products are not. Moreover, proprietary herbal preparations may be adulterated. The public should therefore be careful in interpreting health claims made for herbal products. Because patients may not disclose their history of using herbal anti-obesity products, healthcare professionals should ask specifically about the use of these agents and should report all suspected adverse reactions to their national spontaneous reporting system.

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