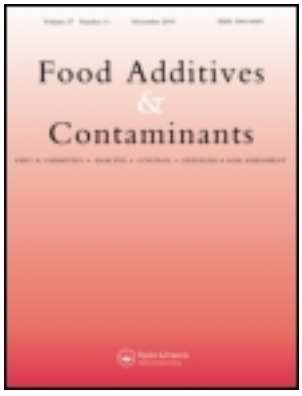

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A new approach to determining pharmacologic adulteration of herbal weight loss products

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A new approach to determining pharmacologic adulteration of herbal weight loss products

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Pharmaceutical adulterants are commonly found in herbal weight loss products, and analytical techniques for detecting these adulterants have become increasingly important to the public health community. Previously we reported a novel analytical method for the determination of adulterants in herbal formulations by capillary electrophoresis with contactless conductivity detection. The current study refines this previously described technique by testing if anxiolytics, diuretics, and laxatives interfered with the detection of anorectics and antidepressants. A survey of herbal weight loss products sold by compounding pharmacies in Brazil were analysed to determine the presence of pharmaceutical adulterants. A total of 106 herbal products, collected from 73 pharmacies in nine Brazilian states, were analysed for amfepramone, sibutramine, fenproporex, fluoxetine, paroxetine, sertraline and bupropion using the new analytical method. The method permitted the rapid and selective screening for the seven adulterants. Of the 106 weight loss products sampled, four (3.8%) were found to be adulterated by fenproporex or sibutramine. The adulterated samples were compounded by four different pharmacies located in three different Brazilian states. The novel capillary electrophoresis method we developed may be a useful tool for public health organisations tasked with analysing herbal weight loss products.

Keywords: adulteration; weight loss products; anorectics; capillary electrophoresis

Introduction

Obesity has been recognised as a worldwide disease that affects millions of people and it constitutes a serious public health problem. Safe and effective weight loss methods are an essential component for addressing the global obesity epidemic, and the cornerstone of treating obesity remains a modest reduction in caloric intake combined with increased physical activity. However, many people seek short-term solutions that promise rapid weight loss such as pharmaceutical anorectics and phytopharmaceuticals (Carvalho et al. 2011a).

Alternative medicine has historically been very popular in developing countries where herbal-based formulations have long accompanied other obesity treatments. According to Brazilian legislation, phytotherapeutic formulations must be obtained exclusively from vegetable raw materials. However, a substance cannot be considered a ''phytotherapeutic drug'' if it includes any synthetic pharmaceutical product (ANVISA 2010b). In addition to phytotherapeutic formulations for obesity, dietary supplements are also marketed for weight loss in Brazil. The current Brazilian legislation defines dietary supplements as foodstuffs that serve to complement the daily diet of a healthy person. ANVISA, the Brazilian equivalent of the US Food and Drug Administration (USFDA), classifies dietary supplements as single or associated vitamins, minerals or natural products (e.g. botanical extracts and fish oils) acting as a source of vitamins or minerals (ANVISA 1998).

Previous studies in Brazil (Auricchio et al. 1991; Almeida et al. 2000; Carvalho et al. 2010a, 2010b) have reported the adulteration of presumably herbal weight loss formulations with anorectics (amfepramone and fenproporex), antidepressants (fluoxetine), and anxiolytics (benzodiazepines). According to the USFDA (2006), these weight loss pills have been exported to the United States and marketed as natural dietary supplements. Case reports have demonstrated the harm of weight loss pills from Brazil when consumed in the United States (Nguyen et al. 2006; Cohen et al. 2009; Smith and Cohen 2010). In two of these cases the synthetic drugs fenproporex, chlordiazepoxide and fluoxetine were identified as adulterants, and users reported headache, palpitations, chest pain, nausea, insomnia and fatigue (Cohen 2009b). Additionally,

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ANVISA banned the sale of various "natural" weight loss products because they were found to have been adulterated with sibutramine (Cohen 2009a; ANVISA 2010a, 2010c, 2010e).

The methods employed for the analysis and quantification of adulterants often make use of separation techniques with universal or selective detectors based on optical (Parodi et al. 1993; Ku et al. 1999; Kanan et al. 2009; Wang et al. 2010) and mass spectrometric methods (Gratz et al. 2004; Reepmeyer and Woodruff 2006, 2007; Venhuis et al. 2008; Chen et al. 2009; Kim et al. 2009; Reepmeyer and d'Avignon 2009; Savaliya et al. 2010). The capillary electrophoretic (CE) methods normally employ UV detection for adulterant analysis (Ku et al. 1995, 1996; Renou-Gonnord and David 1996; Piette and Parmentier 2002; Hancu et al. 2007; Cianchino et al. 2008). The use of mass spectrometry coupled to separation methods is very useful, mainly when the identification of adulterants involves analogues or similar compounds that may demonstrate similar chromatographic patterns (Reepmeyer and Woodruff 2006, 2007; Venhuis et al. 2008; Zou et al. 2008; Reepmeyer and d'Avignon 2009; Singh et al. 2009). However, the identification of species based on their migration or retention times can also be used to confirm the presence of adulterants, mainly in the cases where they have different structures and, consequently, different retention behaviour in the separation systems. Furthermore, the CE methods based on zone electrophoresis (CZE) and conductivity detection exclude the possibility of detecting non-ionic or non-ionisable species in the electrophoretic run, since all these species are carried by the electrosmotic flow in the separation system.

This study assessed the presence of anorectic and antidepressant pharmaceutical adulterants in samples of weight loss products collected from 73 pharmacies in nine Brazilian states. The samples were analysed for seven possible adulterants using an analytical method developed for this purpose which employs CE with electrochemical detection. The results of the analyses are discussed in the context of the current regulatory framework of these weight loss products in Brazil.

Materials and methods

Instrumentation and apparatus

CE measurements were performed using a CE system equipped with a capacitively coupled contactless conductivity detector (C^4D), as described elsewhere (Carvalho et al. 2009). The separations were performed using an uncoated fused-silica capillary tube of 68 cm × 75 μm ID × 360 μm OD (Microtube, São Paulo, SP, Brazil) under an applied voltage of 15 kV. The detection was accomplished using contactless conductivity on the cathode side. The solutes were injected in the hydrodynamic mode from the anodic compartment by gravity after elevating the anodic compartment 20 cm for 60 s. All experiments were performed at 25°C.

Reagents and solutions

Stock solutions of 1 g l^{-1} of anorectics (i.e., amfepramone, sibutramine and fenproporex) and antidepressants (i.e., fluoxetine, paroxetine, sertraline and bupropion) were made in methanol. Working solutions of 50 mg l^{-1} were prepared by diluting these solutions with ultrapure water (Milli-Q, Millipore, Bedford, USA). The working solutions were prepared by diluting the stock solution with methanol. All solutions were stored at −17°C until used and were stable for 1 month.

The working electrolytes were prepared daily and consisted of a 0.05 mol l^{-1} phosphate buffer solution in 50% (v/v) acetonitrile. The pH of the working electrolyte was adjusted using 0.1 mol l^{-1} H_3PO_4. The working electrolyte solutions were filtered through a 0.45 μm membrane filter (Sartorius, Göttingen, Germany) and degassed for 30 min via sonication prior to use.

Samples of weight loss supplements

The Internet was searched for compounding pharmacies advertising herbal weight loss supplements in nine different Brazilian states (i.e., Ceará, Distrito Federal, Goiás, Minas Gerais, Paraná, Rio de Janeiro, Rio Grande do Sul, Santa Catarina and São Paulo). Based on this search, two female research assistants contacted 190 pharmacies by email, telephone or in person to request any available natural weight loss products (including both herbal medicines and dietary supplements). Among the contacted pharmacies, 97 initially responded that they would send the requested formulations. We received via express mail 106 herbal weight loss preparations from 73 pharmacies. These samples were stored at room temperature and used as received for analysis. We documented the labelled components of each weight loss product then analysed the each for adulterants using the described methodology.

Analytical procedures

At the beginning of each day, the silica capillary was rinsed with water for 10 min, 0.1 mol l^{-1} NaOH for 15 min, and water for another 15 min before equilibrating with the working electrolyte for 30 min. After each electrophoretic separation, the capillary was rinsed for 5 min with the working electrolyte.

For the CE determination of the adulterants in the formulations, the average weight of 10 capsules was

measured, and a sample pool was prepared. The equivalent weight of one capsule was then dissolved in 25 ml of methanol in a volumetric flask before filtrating with first cotton and then cellulose acetate membranes (0.45 μm); 1 ml of this solution was then injected into the CE system. The identification and quantification of the adulterants in the samples was accomplished using the standard addition method ($n = 3$).

Results and discussion

Current regulatory aspects of herbal formulations and their consumption in Brazil

It is well known that adding undeclared synthetic pharmaceuticals to dietary supplements or phytotherapeutics violates the laws of many countries (Cohen 2009a). Furthermore, the regulatory framework governing these formulations is very different from country to country (Carvalho et al. 2011b). In previous research we reported the pharmacological classes of undeclared pharmaceuticals found in both dietary supplements and general herbal-based medicines throughout the world (Carvalho et al. 2011a). Not surprisingly, the pharmaceutical class most often found as adulterants in formulations marketed for weight loss are the anorectics including fenfluramine, phentermine, sibutramine, rimonabant, fenproporex, clobenzorex, amfepramone and mazindol.

The registration of herbal medications normally involves an evaluation step concerning their safety, efficacy and quality before allowing the products to be marketed in Brazil (ANVISA 1995). Therefore, manufacturers have to provide this information and standardise botanical formulations based on one compound (e.g. synephrine in *Citrus aurantium*). Since 2003, the herbal medicine industry has been required to implement good manufacturing practices (GMP) (ANVISA 2007). After the new legislation was enacted, a considerable number of herbal medicines already on the market were considered illegal. Many companies found that only a fraction (e.g. 30–35%) of their products complied with the new regulations. However, some producers circumvented the new regulations by using a loophole in the law that considered vegetable extracts to be dietary supplements. Dietary supplements are not obligated by law to follow the same requirements for herbal medicines when registering a new product for the market.

Among the 106 weight loss products received from 73 compounding pharmacies, most of the samples were labelled as containing at least four herbal extracts, which suggests, if the labels are accurate, that a wide variety of natural ingredients are used in these formulations. As shown in Table 1, the most prevalent species was found to be *Caralluma fimbriata*. (Of note, *C. fimbriata* was banned by ANVISA in 2010 (ANVISA 2010d) as a herbal medicine for weight loss due to lack of efficacy.) *C. fimbriata*, *Rhamnus purshiana* and *Fucus vesiculosus* were listed in over 60% of the weight loss products obtained. One-third of the samples listed on the label at least one synthetic substance (i.e., amino acids, vitamins, diuretics and nutrients) (Table 2). These weight loss products with synthetic ingredients are not appropriately marketed as only herbal-based medicines.

Surveys of consumers have demonstrated that some adulterated products can cause weight loss and this is likely due to the pharmaceutical adulterants (Cohen et al. 2012). However, there are many hazards involved with using these products to lose weight. For one, the pharmaceutical adulterants are often produced without any safety controls. Additionally, dosages found in

Table 1. Plant species listed on the label of sampled weight loss products ($N = 106$).

Scientific name	Number of samples with the plant species
Caralluma fimbriata	26
Rhamnus purshiana	23
Fucus vesiculosus	21
Centella asiatica	20
Garcinia cambogia	17
Citrus aurantium	16
Phaseolus vulgaris	14
Cynara scolymus	14
Amorphophallus konjak	13
Camellia sinensis	13
Cordia ecalyculata	12
Equisentum sp.	11
Cassia augustifolia	11
Spirulina maxima	11
Chitosan	10
Slendesta	7
Passiflora sp.	6
Baccharis trimera	5
Gymnema silvestris	5
Gelidium corneum	4
Plantago psyllium	4
Ptychopetalum uncinatum	4
Carthamus tinctorius	2
Cyamopsis sp.	2
Phytolacca decandra L.	1
Cassia nomame	1
Piper nigrum	1
Valeriana officinalis	1
Paullinia cupana	1
Zingiber officinalis	1
Cinnamomum zeylanicum	1
Capsicum sp.	1
Echinodorus macrophyllus	1
Persea americana	1
Ginkgo biloba	1
Arctostaphylos uvaursi	1
Cordia salicifolia	1
Chlorella pyrenoidosa	1

Table 2. Declared synthetic additives on the label of sampled weight loss products ($N = 106$).

Additive classes	Substance	Incidence in the samples (%)
Aminoacids	Triptofan, methionin, carnitine	3
Vitamins	Vitamin B6, folic acid, calcium pantothenate, vitamin E, nicotinamide, vitamin C	10
Nutrients	Betaine, choline bitartrate, potassium aspartate, potassium chloride, collagen, chromium picolinate, inositol	11
Diuretics	Furosemide, hydrochlorothiazide	5
Antiulcer	Ranitidine	2
Stimulant	Caffeine	1
Anaesthetic	Benzocaine	1

adulterated supplements vary widely, sometimes much greater than prescription strength (Cohen et al. 2012). Furthermore, patients often do not inform their physicians that they are consuming herbal supplements, but even when they do, neither the patients nor the physicians caring for them would be aware of the undeclared ingredients. Adverse effects may be due to the pharmaceutical product itself or a drug–drug interaction. In addition, unnecessary medical evaluation that entails its own risks may be performed if adverse effects are not correctly ascribed to the adulterant.

Analysis of anorexic and antidepressant adulterants in herbal weight loss formulations

The development of accurate analytical methods for detecting adulterants in herbal formulations is a very important area of research within the fields of analytical toxicology, pharmaceutical science and forensic science. The number of possible pharmacological products that might be found as adulterants in purportedly "herbal" weight loss formulations is large including anorectics, antidepressants, anxiolytics, diuretics and/or laxatives (Carvalho et al. 2011a). In this context, CE has gained prominence among conventional separation techniques for the analysis of herbal formulations. Previously we reported a novel analytical method for the determination of eight possible adulterants in herbal formulations by CE with contactless conductivity (C^4D) detection (Carvalho et al. 2010b). This method was capable of selectively screening and quantifying amfepramone, fenproporex, sibutramine, fluoxetine, bupropion, sertraline, paroxetine and flurazepam in phytotherapeutic samples. In addition to the efficient separation of the most common adulterants, the combined capability to separate specifically cationic species (through anodic injection) by CE and to detect only appreciably conducting organic species by C^4D permitted a more selective determination of these adulterants than other methodologies.

The optimised method had the following results for the main analytical validation parameters for amfepramone, fenproporex, sibutramine and fluoxetine, respectively: 205.0, 235.0, 265.0, and 205.0 mg kg^{-1} for limits of detection (LOD); 675.0, 780.0, 875.0 and 690.0 mg kg^{-1} for limits of quantification (LOQ); 9.8%, 8.9%, 6.1% and 8.5% for precision (RSD); and 95.4%, 112.4%, 100.8% and 108.9% for accuracy.

The current study refines the authors' previously described techniques by testing if anxiolytics, diuretics and laxatives interfered with the detection of anorectics and antidepressants. None of the tested adulterants, which included anxiolytics (i.e., bromazepam, alprazolam, midazolam, diazepam, chlordiazepoxide, medazepam and lorazepam), diuretics (i.e., furosemide, hydrochlorthiazide, spironolactone, chlorthalidone and amiloride), and laxatives (i.e., phenolphthalein and bisacodil), interfered with the determination of the eight analysed adulterants by the proposed CE method using optimised conditions. The interference of the natural bioactive ingredients from plants was also investigated by injecting non-adulterated industrialised products and pure powdered herbs, which are used by compounding pharmacies for encapsulating herbal medicines or dietary supplements. The injection of these products did not show any of the electrophoretic peaks typically related to the studied adulterants. The only signal observed was the one related to the electroosmotic flow (EOF), which probably included all the neutral molecules present in the obtained herbal extract.

Therefore, all the dietary supplements were first screened for suspicious electrophoretic peaks in the region where the studied adulterants (i.e., amfepramone, fenproporex, sibutramine, fluoxetine, paroxetine, sertraline and bupropion) normally appear under optimised and validated experimental conditions. The presence of the studied adulterants was confirmed by the standard addition, considering the migration times (min) obtained for each adulterant in the sample. In order to attribute the electrophoretic peak to one of the studied adulterants in the sample, a maximal deviation of ±3% for migration times was accepted, since the relative standard deviation of migration times for all the standards separated under optimised conditions (Carvalho et al. 2010b) ranged from 1.93% to 2.81%. After screening all 106 samples, 36% of them were selected for further analysis to confirm and quantify the adulterants via the standard addition method. Among the samples, 3.8% ($n = 4$)

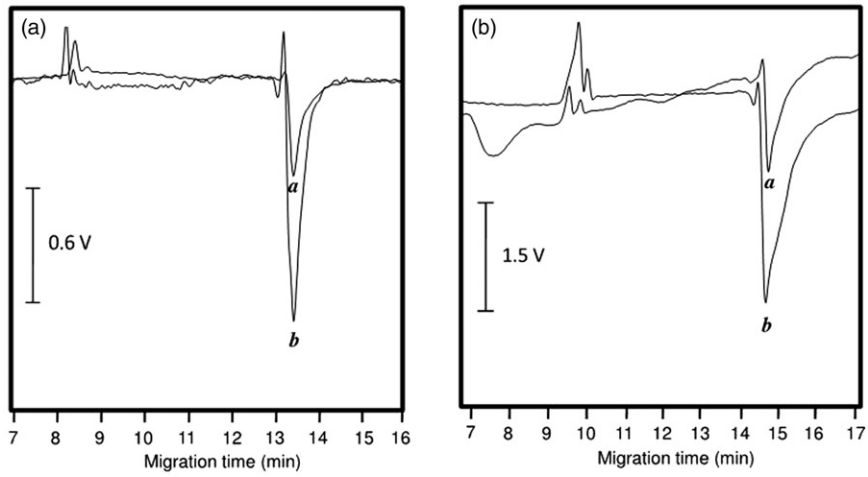

Figure 1. Electropherograms of two samples containing (A) fenproporex and (B) sibutramine as adulterants: (a) sample (dissolved in a 25 ml methanolic extract); and (b) sample plus standard addition of fenproporex or sibutramine (25 mg l^{-1}). Other conditions as described in the ''Materials and methods'' section.

Table 3. Listed ingredients and anorectic adulterants detected in sampled weight loss products.

Sample	Declared sample composition	Adulterant	Concentration (mg kg^{-1})[a]
A	*Glucomanann*, *Garcínia cambogia*, *Valeriana officinalis*, *Plantago psyllium*, *Citrus aurantium*, *Equisetum arvense* L., *Gymnema sylvestre*	Fenproporex	3342.39
B	*Gymnema sylvestre*, phaseolamin, Green tea (*Camelia sinensis*), *Citrus aurantium*, *Caralluma fimbriata*, chitosan	Fenproporex	2412.92
C	*Caralluma fimbriata*, *Garcinia cambogia*, *Gymnema sylvestre*, *Citrus aurantium,* phaseolamin	Fenproporex	3448.98
D	*Fucus vesiculosus*, *Centella asiática*, Green tea (*Camelia sinensis*), Advantra Z (*Citrus aurantium*)	Sibutramine	3563.47

Note: [a]RSD ($n = 3$): 2–8%.

were confirmed to be adulterated by fenproporex or sibutramine, as shown in the electropherograms in Figure 1. The four adulterated samples were compounded by different pharmacies, which were located in three different Brazilian states. The non-identified peaks observed in the other 32 samples could be related to other adulterant classes or metabolites/analogues of anorectics, which are not detectable by this method. Table 3 presents both the composition declared on the label as well as the concentration of adulterants found by the analyses.

From a clinical point of view, the quantities of fenproporex and sibutramine detected were relatively low compared with prescription dosages; however, the adverse effects of these drugs should still be considered. Sibutramine can cause side-effects in both the nervous system, such as dry mouth, headache, numbness and paresthesias, as well as the gastrointestinal system, such as nausea and constipation. However, its effects on the cardiovascular system are most worrisome. Sibutramine may increase the heart rate and pulse as well as increase the risk for myocardial infarctions and stokes (James et al. 2010). Additionally, fenproporex can produce central and peripheral nervous system stimulant effects, such as vasoconstriction, increased cardiac contractility, bronchodilation, mydriasis, urinary bladder sphincter contraction and increased mental alertness (Haller 2004).

Finally, it is important to emphasise some limitations concerning the sampling method used in this work. First, the results are not necessarily representative of pharmaceutical adulteration of herbal weight loss products throughout Brazil for several reasons, including the fact that the contacted pharmacies may have sent products that were more or less likely to be adulterated; that only a portion of pharmacies (approximately 51%) responded to the initial contact; and that the majority of the samples were received from pharmacies located in only five of the Brazilian states.

Conclusions

This paper has documented that unethical pharmacists continue to adulterate ''herbal'' weight loss products

with pharmaceuticals. The detection of these potentially dangerous adulterants is an important area of active research. The development and refinement of new analytical methodologies that are capable of detecting the common adulterants in these products is becoming increasingly relevant from a regulatory and clinical perspective. The CE method presented in this paper permitted the rapid and selective screening for the adulterants amfepramone, sibutramine, fenproporex, fluoxetine, paroxetine, sertraline and bupropion in the 106 samples analysed, which would be very useful for inspecting commercial dietary supplement formulations by governmental organisations.

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