

WEIGHT LOSS FOOD SUPPLEMENTS: ADULTERATION AND MULTIPLE QUALITY ISSUES IN TWO PRODUCTS OF CHINESE ORIGIN

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Abstract

One of the most serious quality issues associated with herbal products used for healthcare purposes is the deliberate adulteration with synthetic substances, meant to increase the efficacy of respective products in the claimed indications. Here we report on adulteration with sibutramine and phenolphthalein in two herbal food supplements of Chinese origin, widely distributed through internet in various countries, promoted for weight loss. An HPLC method developed and validated by the authors was used for the separation and assay of the two substances. The average content per capsule for one of the two products, determined through this method was 24.71 mg sibutramine and 48.20 mg phenolphthalein. We also determined flavonoids (through a spectrophotometric method), uniformity of mass (according to European Pharmacopoeia, 6th edition) and performed a microscopical examination of the capsule content. The results raised concerns regarding the quality of the two products. Furthermore, an analysis of the clinical and non-clinical data available in the scientific literature for the herbal ingredients of the two products has shown that it is very unlikely that, in the amounts of the current formulations and posology, the products have weight loss inducing effects.

Rezumat

Una dintre problemele de calitate cele mai grave specifice produselor pe bază de plante utilizate în îngrijirea sănătății o reprezintă falsificarea deliberată cu substanțe sintetice, destinată să crească eficacitatea produselor respective în indicațiile în care sunt promovate. Lucrarea de față descrie falsificarea cu sibutramină și fenolftaleină a două suplimente alimentare pe bază de plante, de origine chineză, distribuite pe scară largă prin intermediul internetului în diferite țări și promovate pentru pierderea în greutate. Pentru separarea și cuantificarea celor două substanțe s-a utilizat o metodă HPLC dezvoltată și validată de autori. Conținutul mediu pe capsulă pentru unul dintre cele două produse, determinat prin această metodă a fost de 24,71 mg sibutramină și 48,20 mg fenolftaleină. S-au determinat și flavonele (printr-o metodă spectrofotometrică) și uniformitatea masei (conform Farmacopeei Europene, ediția a 6-a) și s-a efectuat un examen microscopic al conținutului capsulelor. Rezultatele generează îngrijorări cu privire la calitatea celor două produse. Mai mult, o analiză a datelor clinice și non-clinice disponibile în literatura de specialitate pentru ingredientele vegetale ale celor două produse a arătat că este foarte puțin probabil ca, în cantitățile din formulele actuale și cu posologia actuală, produsele să poată induce pierderea greutății corporale.

Keywords: food supplements, sibutramine, phenolphthalein

Introduction

Herbal products are increasingly used for healthcare purposes, worldwide, mainly because of the belief (reinforced by advertisements and promotional techniques) that natural products are effective and safe (free from adverse effects) or safer than conventional medicines obtained by synthetic processes. Besides more traditional preparations (infusions, decoctions, medicinal wines), herbal products are often marketed as food supplements [29]. However, multiple quality problems are associated with their manufacturing and placing on the market (issues related to the identity of the source plants, standardization, contaminations with pesticides or heavy metals, inappropriate labelling in a lax regulatory framework) [27]. One of the most serious quality issue associated with herbal products used for healthcare purposes is the deliberate adulteration with synthetic substances, meant to increase the efficacy of respective products in the claimed indications. Between 2008 and 2009, undeclared drug substances were found in over 70 weight loss supplements in the United States [17]. Cases of adulteration with synthetic substances of various herbal food supplements have also been reported in Europe [11, 20] and other regions of the globe [27].

Various products marketed – especially via the internet, but not only - as "phytotherapeutic products", "traditional medicinal products" or "food supplements" to support weight reduction (such as Best-life[®], Evolution Slim&Slender[®], Meizitanc[®]) have been reported as containing sibutramine and phenolphthalein [21]. Several fatal cases [19, 21] and a higher number of non-fatal intoxications [23] with sibutramine from such products have been reported. In this paper we report on an investigation of two such food supplements of Chinese origin acquired from the Romanian market (but distributed worldwide), which identified the adulteration with sibutramine and phenolphthalein (put into evidence with an HPLC method developed and validated by the authors), as well as multiple quality issues: very large variations in flavonoid contents, an undeclared excipient (maize starch), unacceptable uniformity of mass and lack of a scientifically formulation and labelling.

"*Capsula de slăbit*" (the *Weight-loss capsule*, hereafter CS) and "*Super Slim*" (hereafter SS) are two of the most popular food supplements explicitly designed to help the loss of body weight. Based on a number of interviews carried out in 2009 and 2010 with persons selling these products in herbal outlets in Bucharest, these proved to be among the most highly recommended, one of the sellers also stating that he had "no other effective

products” available in addition to these two brands. We have been prompted to scientifically investigate these products by suspicions relating to adverse effects of these food supplements, reported by patients in pharmacies, as well as through various forums on the internet. By reading the declared composition on their labelling, it seemed very unlikely that such adverse effects (palpitations, sleeplessness, headaches, xerostomia etc.) were caused by the apparently benign compounds contained by these products. Therefore, we suspected that they might contain some amphetamine derivatives. While working on the detection of a potential synthetic adulterant in the two food supplements, in June 2009, the Bucharest Public Health Directorate made public its intention to withdraw the SS product from the market, following a rapid alert from the Belgian authorities, who had detected sibutramine in this product [8]. This led us to also check for the content of sibutramine in the CS; while working on an HPLC method for its separation and detection, a small amount of capsule powder accidentally entered into contact with some detergent and changed its colour to pink; we supposed that it probably also contained phenolphthalein, which was indeed confirmed through HPLC. SS also contained phenolphthalein, even though the information publicly released based on the Belgian rapid alert only mentioned sibutramine as an adulterant. Next, we discovered that public authorities in other parts of the world (the FDA in the United States [18], the MHRA in the United Kingdom [22]) also revealed the detection of sibutramine and phenolphthalein as adulterants in certain food supplements, however not stating the respective amounts found in these products.

Thousands of patients have probably used these products; after withdrawal of SS from the Romanian market, CS continued to be a best-seller among food supplements on the same market. It seems that even SS has continued to be sold through the internet. Moreover, similar products have been and continue to be sold (over the internet at least, if not through physical outlets) in various parts of the world, including Europe (Ireland [7], United Kingdom [4, 9]), the United States [6], Australia [3], Canada [5] and Hong Kong [30]. This extends the level of interest of our findings in this paper from purely national to general.

A team of researchers from China have described the analysis of six synthetic adulterants in herbal slimming food supplements by a validated LC electrospray ionization-MS, including sibutramine and phenolphthalein. In this method, retention times for phenolphthalein and sibutramine were 5.14 and 13.44, respectively [31]. While we were writing this paper, researchers from the French agency AFSAPS published a study reporting on an ultra-high-pressure liquid chromatography (UHPLC) developed for

(simultaneous) detection and assay of 32 potential adulterants of food supplements, including sibutramine and phenolphthalein. With this method, retention times for the two substances were of 6.22 and 6.64 minutes, respectively. Besides, in this latter method, due to the high number of analytes to be separated and assayed, a non-conventional validation procedure was used, which did not investigate the accuracy or precision [26]. We have independently developed and validated an HPLC method for the simultaneous determination of sibutramine and phenolphthalein in herbal food supplements, with still shorter retention times for the two substances than those published up to date: 1.33 and 2.01 minutes, respectively. The proposed method is characterized by an easy sample preparation procedure, a very short assay time and a good applicability.

Not only are the two products adulterated with synthetic substances, but sibutramine is added in an amount twice that used in the past in approved medicinal products containing sibutramine. While mass uniformity is not a requirement for food supplements, considering the presence of the synthetic sibutramine in these products, we investigated the mass uniformity for the two products and found that for CS, the results were out of specification (result which translates into a higher risk for patients). Besides using HPLC to detect and quantify the two adulterants, we here show that assuming the two food supplements were not adulterated, they still have other quality shortcomings: flavonoid contents is highly variable and an excipient is undeclared on the product label. Finally, the formulation (the list of herbal ingredients and their quantities) is not scientifically supported by clinical data.

Materials and Methods

A Varian HPLC system has been used, equipped with a Prostar 240SDM quaternary high-pressure pump and diode-array detector (PDA, Prostar 3309). The two compounds were separated using a CN Nucleosil column (Macherey-Nagel), 100-5 CN, 125 x 4.6 mm. The analytical column was protected with a guard column CN, 10x4.6, packed with 5 μ m particles.

Merck KGaA gradient-grade acetonitrile and methanol for liquid chromatography, as well as ortho-phosphoric acid 85% of analytical grade were used. Potassium dihydrogen phosphate was of analytical grade, purchased from Riedel de Haën. Phenolphthalein used as reference substance was provided by Merck KGaA; sibutramine working standard was kindly provided by Zentiva SA (Bucharest, Romania).

CS, batch no. 290909 and SS, batch no 090203, were purchased from a community pharmacy in Bucharest in 2010.

A Nikon Labophot-2 light microscope equipped with a Nikon digital photo camera was used for the microscopical examination of the powder.

Sibutramine and phenolphthalein were identified and assayed through an HPLC method appropriately validated, as detailed below. We tried to separately identify the flavonoids contained in the capsule formulation through HPTLC (using powder from 5 capsules), but without being successful, probably because of the very low content (500 micrograms per capsule). Flavonoids were assayed using a spectrophotometric method based on the chelating reaction with aluminium chloride, according to the Romanian Pharmacopoeia (10th Edition, *Cynarae folium* monograph) [2], with a standard calibration curve obtained using rutin.

A microscopical examination of the powder was performed using distilled water as a mountant (to avoid inducing a chemical change in the adulterants or components of the powder, we have avoided the use of clarification agents or reagents; our primary interest was assessing whether adulterants could be detected microscopically). Uniformity of mass was determined on 20 capsules according to the European Pharmacopoeia, 6th edition [1].

The product formulation and the leaflet accompanying the packages of the two food supplements, as well as the advertisements on the Romanian websites promoting the capsules were compared with the available scientific literature (identified through computerized interrogations of the Medline database, using appropriate keywords) and critically analyzed. Because no official system of phytovigilance is available at the national level, we have searched internet forums or similar online instruments containing consumer feed-back or experience with the products, in order to estimate the potential adverse impact of the products on human consumers.

HPLC-conditions

The mobile phase consisted of two solvents: (A) potassium phosphate buffer pH 4 and (B) acetonitrile. The phosphate buffer was prepared by adjusting to 4 the pH of a 0.025 M solution of KH₂PO₄. The separation was carried out in isocratic conditions: 65% A, 35% B. The flow rate was 2.5 mL/min, the injection volume was 20 µL and the column temperature 25°C.

The compounds of interest (sibutramine, phenolphthalein) were identified by comparing their retention time values (t_R) and UV spectra with those of the reference substances. For each peak, spectral purity was checked by evaluating available DAD data using the “peak purity” option in the Varian MS Workstation ver. 6.9.1. software.

Sample preparation for HPLC

The contents of 20 capsules were mixed. A quantity of powder containing about 8.5mg of sibutramine or 16.5mg phenolphthalein was accurately weighed in a volumetric flask. 75mL of methanol were added and sonicated for 10 minutes. After 30 minutes, the sample was diluted to volume with methanol and mixed. From the supernatant of the resulting suspension, appropriate dilutions were made so as to obtain solutions of a concentration in the range covered by the calibration data. A portion of the final solution was filtered through a 0.2 μ m filter and injected into the chromatograph.

Validation of the HPLC assay method

Standard stock solutions of the two reference standards (sibutramine and phenolphthalein) were prepared by dissolving them in methanol. These were then diluted with methanol to five concentrations for construction of calibration plots in the ranges of 46.05-92.12 and 27.22-56.7 μ g/mL for sibutramine and phenolphthalein, respectively. The stock solutions were stored at 4°C.

The linearity of the concentrations *versus* peak areas plot for both substances was investigated by computing the regression equations and correlation coefficients; for each compound, the linearity was determined in triplicate. Detection limits (LODs) and quantification limits (LOQs) of the investigated compounds were estimated as the minimum concentration giving a signal-to-noise ratio (S/N) of 3 and 10, respectively; the computation of the two limits was based on the standard deviation of the regression line and slope of the calibration curve. Accuracy was determined by adding three individual concentrations of standard compounds to a solution obtained from the sample capsule powder, so as to get three different concentration levels (low, medium and high spike) and, after analysis, the values obtained were compared with theoretical amounts (subtracting the amounts already available in the capsule powder); three analyses were carried out for each level and results were expressed as the mean of the three analyses. The precision of the method was evaluated by running three replicate samples at three different concentration levels; analyses on each level were performed in a different day, so as to cover both intra-day and inter-day precision (for the inter-day precision, the relative standard deviation for all 9 samples was computed). The processes of the measurements were carried-out according to the "Sample preparation" section.

Results and Discussion

Development of the HPLC method

The chromatographic method was developed and optimized trying several stationary phases, mobile phases and flow-rates. Two stationary phases (C18 and cyano) were used and the best resolution was obtained with a Macherey-Nagel CN Nucleosil column.

With regard to the mobile phase, we have tested acetonitrile, methanol and tetrahydrofuran (THF) with various pH buffers on the C18 column, but the results were not satisfactory: acetonitrile was associated with conspicuous peak tailing, methanol produced both fronting and tailing, while THF lead not only to a rather broad and distorted peak, but also to a considerably long run time. Acetonitrile on a CN Nucleosil column was the only one with optimum results in terms of both resolution and run time. While a pH=5 phosphate buffer required a long run time with some tailing, lowering the pH of the phosphate buffer to 4 assured an appropriate separation with a few minutes run time. In figure 1, separation of the two compounds under optimized HPLC conditions is presented; both compounds were accurately separated within less than 5 minutes. Figure 2 shows a typical chromatogram obtained for the capsule powder (CS). Resolution (R) was higher than 2.0 and the tailing factor calculated at 5% according to USP/EP was less than 1.5.

The optimal wavelength for HPLC analysis was determined to be 225 nm, allowing the sensitive detection of both sibutramine and phenolphthalein. We have also used a second wavelength for the possible detection of natural compounds from food supplements (e.g. polyphenolic compounds), but in the end this did not prove very useful for the purposes of our analysis.

Validation of HPLC method and assay results for CS

Linearity data for sibutramine and phenolphthalein are given in Table I. Signal linearity was confirmed for an interval of 46.05-92.12 and 27.22-56.7 μ g/mL for sibutramine and phenolphthalein, respectively; correlation coefficients (r) were of 0.9996 or higher for sibutramine and 0.9991 or higher for phenolphthalein. At the concentration levels found for sibutramine and phenolphthalein in the two food supplements, interferences due to the analytical matrix seem insignificant. Because pure matrices (without the two synthetic substances) were not available to us, we have not been able to investigate selectivity in a more rigorous manner.

Table I

Linearity data for sibutramine and phenolphthalein: regression equation (Y corresponds to the peak area, X to the amount in $\mu\text{g/mL}$), correlation coefficient (r), linear range ($\mu\text{g/mL}$), limit of detection (LOD) ($\mu\text{g/mL}$), limit of quantitation (LOQ) ($\mu\text{g/mL}$) and range ($\mu\text{g/mL}$).

Substance	Regression equation	r	LOD $\mu\text{g/mL}$	LOQ $\mu\text{g/mL}$	Range $\mu\text{g/mL}$
Sibutramine	$Y=16.968X - 12.466$	0.9999	1.34	4.47	51.2-92.12
	$Y=17.135X + 56.399$	0.9997	2.01	6.71	50.68-91.22
	$Y=15.613X + 126.000$	0.9996	2.34	7.81	46.05-82.89
Phenolphthalein	$Y=42.577X+1.900$	0.9996	1.51	5.02	31.50-56.70
	$Y=39.951X+23.300$	0.9998	1.10	3.66	30.42-54.76
	$Y=39.749X+158.300$	0.9991	1.98	6.61	27.22-49.00

Analysis of the precision of the intra-daily (three times a day, in three different days) and inter-daily (in three different days for all nine measurements performed) showed that the relative standard deviation (R.S.D. or coefficient of variation, CV) was less than 3.41% for both compounds (table II).

Table II

Precision of the intra-daily and inter-daily HPLC measurements for sibutramine and phenolphthalein

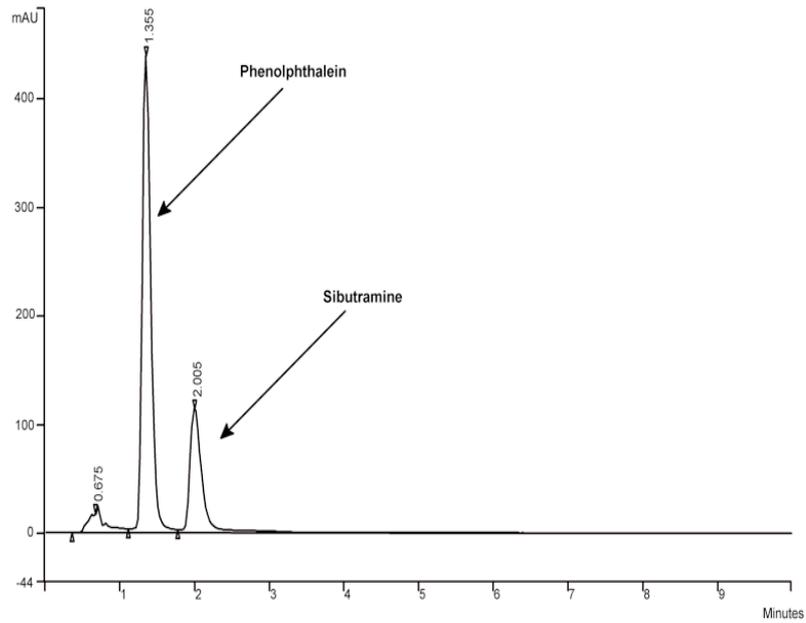
Substance	Level	Contents (%)	Intraday R.S.D. (%)	Inter-day R.S.D. (%)
Sibutramine	1	9.92 \pm 0.34	3.41	2.98
	2	9.69 \pm 0.26	2.64	
	3	9.57 \pm 0.24	2.51	
Phenolphthalein	1	18.59 \pm 0.12	0.62	2.27
	2	19.50 \pm 0.22	1.11	
	3	18.83 \pm 0.11	0.58	

Recovery rates ranged between 98.75% and 100.51% on all three spiked levels, hence within the typically accepted limit of $100 \pm 5\%$ (Table III).

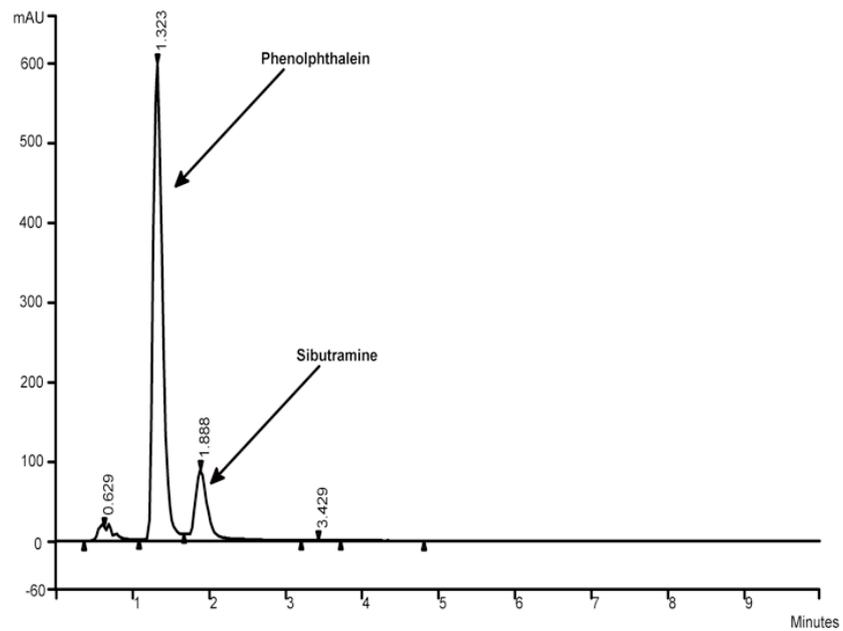
Table III

Accuracy of the HPLC assay method, using spiking and recovery experiments (three spike levels); values expressed in $\mu\text{g/mL}$

Level	Compound	Total $\mu\text{g/mL}$	Spiked (theoretical) $\mu\text{g/mL}$	Spiked (found) $\mu\text{g/mL}$	Recovery (%)
Low	Sibutramine	54.79	33.78	33.57	99.38
	Phenolphthalein	31.50	12.60	12.43	98.75
Medium	Sibutramine	73.07	40.54	40.75	100.51
	Phenolphthalein	39.89	7.30	7.34	100.47
High	Sibutramine	86.85	45.49	45.33	99.64
	Phenolphthalein	54.35	9.74	9.71	99.68

**Figure 1**

Typical chromatogram obtained with reference substances under optimized HPLC conditions

**Figure 2**

Chromatogram obtained with capsule content of an adulterated for the food herbal supplement (CS)

The average content per capsule determined through this method was 24.71 mg sibutramine and 48.20 mg phenolphthalein (97.28 mg g⁻¹ and 189.76 mg g⁻¹, respectively). It is interesting to notice that the amount of sibutramine found in our assay is almost twice the maximum concentration of the products authorized in the past as medicinal products (such as Reductil[®] and its generics); these products used to contain 10-15mg/capsule. In the European Union, considering the recommendation of the European Medicines Agency [16], sibutramine containing products were withdrawn from the market in 2010. The usual dose for sibutramine was 10 mg daily, which could be increased to 15 mg daily after 4 weeks. The assay results show that not only the product contains an undeclared ingredient, but its amount is also well over the usual recommended dose (a consumer/patient will start directly with almost 25 mg instead of 10; this probably explains the high percentage of adverse effects reported for this “food supplement”). H. Rebiere *et al.* (2012) analysing 32 commercial slimming formulations in France detected sibutramine in 9 of them, and sibutramine content varied between traces and 30 mg per dosage unit [26]. Wang J. *et al.* (2008) analysed 22 food supplements from China and found 11 of them adulterated with various substances; sibutramine was found in 10 of these samples, also with a varied content, but the maximum amount found in one of the products was 96.2 mg g⁻¹[31], which indicated that sibutramine content in CS was among the highest in the samples for which published results are available.

Phenolphthalein was a common ingredient in various laxatives for most of the 20th century to the late 1990's, when the United States Food and Drug Administration (FDA) changed its classification in OTC drug products as “not generally recognized as safe” [14]. Following this measure, phenolphthalein based medications went out of market and use in the EU and other countries in the world. The FDA initiative was based on evidence from non-clinical studies in rodents, in which two year administration of phenolphthalein was shown to induce cancers at multiple sites and organs (kidney, adrenal medulla, ovary) [14, 15]. Other animal or *in vitro* studies showed that phenolphthalein is genotoxic [28], inducing chromosome aberrations, probably mediated by free radicals and oxidative stress [10]. In all these non-clinical experiments the doses used were much higher than the therapeutic human dose. Epidemiological studies failed to confirm that phenolphthalein is carcinogenic in humans; nonetheless, they have not addressed the risks of the intense use or abuse, but rather occasional or low(er) dose use [13, 14]. The usual phenolphthalein oral dose as an OTC laxative for adults was 30 to 200 mg, not to exceed 270 mg [24]. Hence, the

amount of phenolphthalein found as an adulterant in CS (48.20 mg per capsule) is closer to the lower dose and the risks of its presence seem lower than those associated with sibutramine (although the risk of carcinogenicity after prolonged use cannot be completely ruled out). In other published reports, phenolphthaleine was less detected as an adulterant: 4 (two brands only) of the 32 formulations analysed by H. Rebiere *et al.* (2012) [26], 3 of 22 supplements examined by Wang J. *et al.* (2008) [31].

Flavonoid assay: For CS, an average content of 217.44mg per 100g of powder (202.21-232.67mg per 100g) and for SS 301.68 mg (361.71-372.53mg) of flavonoids (expressed as rutin) per 100g of powder have been found. On the label of both products a minimum level of 200 mg flavones per 100g is stated by the manufacturer, therefore both are in line with the specification. It is to be seen, though, that while in the case of CS the values determined are fairly close to the minimal amount specified, in the case of SS the level found is about 50% higher than the value specified. From the information included in the leaflet and promotional materials, as well as from careful analysis of the formulation, there is no justification for the use of flavones for standardization or quantification purposes in this case. European regulatory authorities make a distinction between standardised and quantified herbal substances or preparations. “*Standardised* herbal substances/herbal preparations are adjusted to a given content of constituents with known therapeutic activity within an acceptable tolerance; standardisation is achieved by adjustment of the herbal substances/herbal preparations with excipients or by blending batches of herbal substances and/or herbal preparations. *Quantified* herbal substances/herbal preparations are adjusted to a defined range of constituents (active markers); adjustment is exclusively achieved by blending batches of herbal substances and/or herbal preparations“ [12]. None of these two hypotheses seem to be applicable for the two products. Not all components of the two food supplements contain flavones, and thus, for those components, the flavones do not in any way control the uniformity and quality of the products. Besides, although a minimal amount of 200 mg flavones per 100 g of product is declared, it is not stated what specific flavone molecule is used for standardization or quantification purposes (the group of flavones is very diverse and these are assayed globally and expressed in a single flavone molecule, such as rutin).

Results of microscopical examination. We have not been able to detect the synthetic powders (sibutramine, phenolphthalein) by microscopy. Representative photomicrographs of the images seen for the powder of CS, as well as for SS are shown in figure 3.

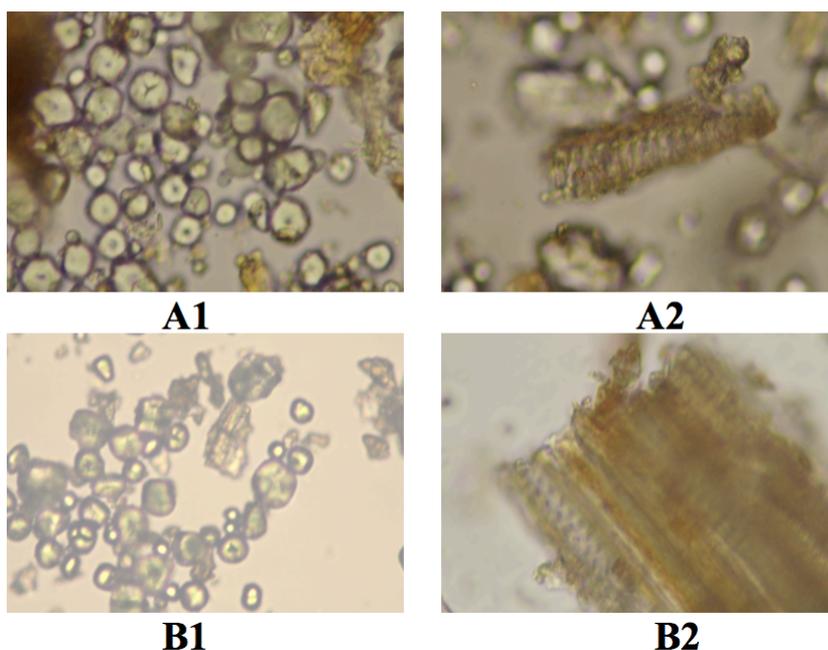


Figure 3

Microphotographs of powder from CS (A) and SS (B): starch grains (probably from *Zea mays*) (1) and large caliber xylem vessels fragments (2)

The images are fairly comparable for the two products, suggesting that they are sufficiently similar or even identical. The formulation stated on the labels is very similar, with a single exception: the CS label states “*Dioscorea esculenta* extract”, while the SS label reads “cellulose from *Dioscorea*”. The microscopical images suggest that this may be rather a translation/typographical error than a true difference, because all the ingredients and their proportions are otherwise identical. Numerous starch grains and relatively frequently small fragments of plant tissues were seen; fragments of fibers (possibly cellulose or sclerenchyma) and large calibre xylem vessels (reticulate and pitted) were only rarely observed.

It is worth mentioning that the starch grains generally dominating the microscope field are very similar with the maize ones (*Zea mays* L., Poaceae), although maize starch is not declared among the ingredients. It is unlikely that these starch grains should come from the other powder ingredients of the formulation. The presence of undeclared maize raises an uncertainty regarding the proportions stated for the other ingredients; also taking into account the undeclared sibutramine and phenolphthalein, this uncertainty is even stronger.

Uniformity of mass results. In principle, for food supplements, uniformity of mass is not a requirement (the European Pharmacopoeia provides that „the test is not required for multivitamin and trace-element preparations and in other justified and authorised circumstances”). In the light of the high sibutramine contents of CS, though, mass uniformity becomes relevant and this is the reason for which we have undertaken this simple test. According to the European Pharmacopoeia, for capsules with a content of less than 300 mg (as is the case for CS and SS), not more than 2 of the individual masses may deviate from the average mass by more than 10%. Our results showed that, for CS, 4 individual masses deviated from the average mass (+10,10%, -11.67%, -15.26% +12.62%), thus being out of specification; in the case of SS, we have found only one such deviation (+13.86%), this product being thus within the specification regarding this parameter. Results of the distribution of the individual masses are shown graphically in figure 4. Considering that the amount of sibutramine is already much higher than the dose formerly recommended for therapeutic purposes, the fact that two of these deviations are positive (i.e. higher with over 10% than the average) is an additional point of concern.

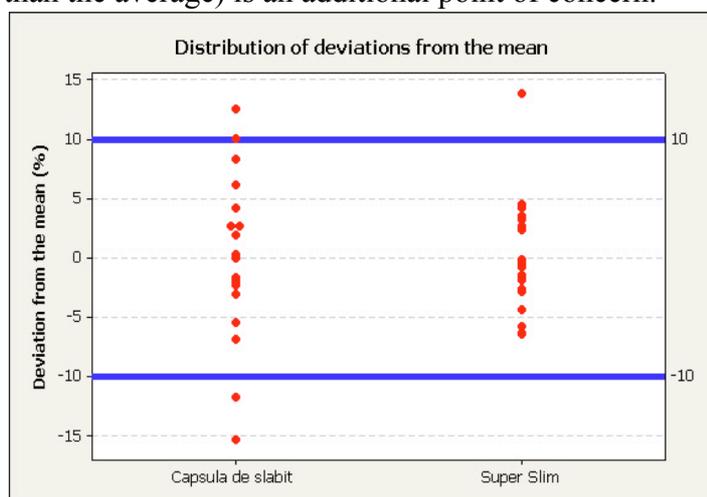


Figure 4

Uniformity of mass results for the two food supplements

Critical analysis of the formulation and product information.

A critical analysis of the formulation and product information in the light of the published scientific literature showed that none of the ingredients has been proven clinically effective and the amounts used in this formulation are much lower than those used in non-clinical or clinical trials. Because of editorial constraints, details of this analysis are available on the

website: www.botanica-farmaceutica.ro . All ingredients are derived from edible plants and have not been reported to have any significant safety risks. Despite of this innocuous composition, surprisingly though, the two food supplements are contraindicated in “children up to 14 years, pregnant or lactating women, persons with cardiovascular conditions (or other diseases associated with these conditions), diabetes mellitus and kidney diseases”. In the light of their apparently harmless composition, it is also difficult to understand why the posology is limited to a single daily dose. This seems to reflect the sibutramine posology (once a day) and contraindications (children, pregnant and lactating women, cardiovascular and kidney diseases) rather than any clinical or non-clinical data on the components of the two supplements, which allows one to think that adulteration might have been deliberate.

Conclusions

The presence of the two adulterating substances (sibutramine and phenolphthalein) is a serious cause for concern, because this is not an accidental contamination, but an intentional act. Moreover, while counterfeiting may take place at various levels of the supply chain, in this case an intentional adulteration by the genuine manufacturer itself seems possible (as suggested by the restrictive posology and contraindications, which would otherwise make no sense). Irrespective of the intentional or accidental character of the falsification, the use of such products may lead to serious adverse reactions or unwitting doping with sibutramine (amplifying an already worryingly high tendency of deliberate use of doping substances by sportspersons) [25].

Sibutramine medicines have been withdrawn from the market due to the suspension of the marketing authorization; paradoxically, it is sold, however, without the knowledge of the consumer, in large amounts, as food supplements. The paradox lies in that medicines are assumed to be higher risk products and subject to rigorous control. By law (and by society implicitly), food supplements are assumed to be harmless products that only supplement human food and hence are loosely regulated in most countries, usually through a simple notification process. Another side of the same paradox is that, while the composition and *all* adverse effects of a medicine are declared, in the case of food supplement adulteration the consumer is not aware that these adulterants are there at all. Sibutramine containing medicines targeted a narrow part of the population, the treatment being initiated by a doctor only (because only in that specific population the benefits were deemed higher than the potential risks); in the case of

adulterated food supplements, though, sibutramine reaches the general population, where its risks may outweigh its benefits.

A computerized investigation on Romanian internet forums identified over 100 persons reporting adverse events after the use of one of the studied products. The most frequent adverse events in CS users were dizziness, abundant sweat, palpitations, high blood pressure or other cardiac disorders, headaches, xerostomia and thirst, insomnia, fatigue, agitation and nervousness, nausea, "dark thoughts" (suicidal ideation), breathing difficulties and vision disorders. For SS, adverse events were similar: dizziness, excessive perspiration, thirst and xerostomia, headaches, fatigue, insomnia, high pulse rate, dyspnoea, lump feeling in the throat, increased blood pressure, restlessness and nervousness, vision disorders, depression, paresthesias and nausea. These are in line with the known adverse events of sibutramine and phenolphthalein, especially of the former.

The increasing number of adulteration reports in the past years all over the world, as well as other quality deficiencies (as shown in this paper) should prompt regulators to think of new paradigms of approval and market surveillance of dietary supplements in order to protect the public from potential harm associated with adulteration, unscientific formulations and inappropriate labelling and promotional practices.

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