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Detection of Adulterants in Herbal Weight Loss Supplements

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Abstract: The growing popularity and consumption of herbal slimming supplements can be attributed to their perception as natural products that lack side effects. However, the composition and ingredient quality listed on their labels often undergo insufficient control. As a result, some manufacturers add undeclared synthetic pharmaceuticals to enhance weight loss effects. The synthetic adulterants, particularly the anorectic stimulants, have been associated with increased risks of cardiovascular adverse effects, posing significant health risks to consumers. This study aimed to analyze various weight loss supplements marketed as "natural" products to detect possible adulterants. A new high-performance thin-layer chromatography (HPTLC) method was used for initial screening, while gas chromatography coupled with mass spectrometry (GC–MS) served as a confirmation tool. Additionally, high-performance liquid chromatography (HPLC) was employed to analyze phenolphthalein. A total of 34 supplements acquired online or from specialty stores were analyzed. It was found that most of them contain caffeine from herbal ingredients included in the products' formulation. Some products list the added caffeine, but the measured levels significantly exceeded the labeled values. The most commonly detected adulterants were sibutramine and phenolphthalein. These results highlighted the inadequacies and inconsistencies in labeling, as all herbal supplements were declared "natural" despite containing adulterants. Furthermore, they highlighted the suitability of the HPTLC method as an effective and cost-effective screening tool for detecting adulterants in dietary supplements.

Keywords: adulterants; dietary supplements; sibutramine; caffeine; phenolphthalein; HPTLC; GC–MS

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1. Introduction

Overweight and obesity are defined by the World Health Organization (WHO) as abnormal or excessive fat accumulation that presents a risk to health. A body mass index (BMI) over 25 kg/m^2 is considered overweight, and a BMI over 30 kg/m^2 is considered obese. Overweight and obesity are chronic metabolic diseases currently classified as an

epidemic; in 2022, 2.5 billion adults (18 years or older) were overweight, including over 890 million who were obese. Complications and comorbidities related to obesity include cardiovascular diseases such as heart disease and stroke, dyslipidemia, diabetes, and musculoskeletal disorders, including osteoarthritis. Obesity is also associated with some cancers, including those of the endometrium, breast, ovary, prostate, liver, gallbladder, kidney, and colon [1,2].

First-line intervention should include behavioral changes, dietary restriction, and the introduction of physical activity. Pharmacological intervention is advised for patients with BMI $\geq$ 30 kg/m^2, while bariatric surgery is recommended for patients with BMI $\geq$ 40 kg/m^2 or patients with BMI $\geq$ 35 kg/m^2 with coexisting obesity-related comorbidity [2]. As people look for lighter alternatives, the demand for weight loss supplements and medicines has increased.

Furthermore, maintaining a healthy weight and attractive physical appearance are highly valued in today's culture. Despite this, many people find it difficult to accomplish these goals on their own, as it takes time and effort to make the necessary dietary, exercise, and lifestyle changes. Food supplements that offer a quick fix in these circumstances can be seen as an effective remedy [3]. About 15% of American people report using dietary supplements for weight loss at some point in their lives; women report using these supplements more frequently than men (21% vs. 10%) [4]. One of the top 20 reasons that people take dietary supplements is to lose weight, with Americans spending approximately USD 2.1 billion annually on weight loss pill forms (e.g., tablets, capsules, and soft gels) [4]. Most of these supplements contain plants or plant extracts [4]. The most common components of dietary supplements for weight loss are listed below.

Caffeine and herbal sources that naturally contain caffeine, such as guarana (*Paullinia cupana*), kola (or cola) nut (*Cola nitida*), and yerba maté (*Ilex paraguariensis*), stimulate the central nervous system, heart, and skeletal muscles. They also function as diuretics and raise colonic and stomach activity. In humans, caffeine enhances thermogenesis in a dose-dependent and linear manner. It also aids in weight loss by promoting fluid loss and fat oxidation via sympathetic nervous system activation. However, regular caffeine use causes tolerance and a reduction in these benefits [5].

Paullinia cupana, commonly known as guarana, is a plant well-known for its caffeine content, making it a popular ingredient in weight loss supplements. It contains tannins, saponins, and catechins, which may help to reduce oxidative stress. Dosages vary, but 50–200 mg of caffeine per day is common for energy-boosting effects [6].

Garcinia cambogia is a tropical fruit also known as Malabar tamarind. It is commonly used as a weight loss supplement due to its active ingredient, hydroxycitric acid (HCA), which is believed to help to suppress appetite and inhibit fat production by blocking citrate lyase, an enzyme involved in fat production [7].

Bitter orange (*Citrus aurantium*) fruit contains various protoalkaloids and *p*-synephrine (a stimulant), which is often known as synephrine. The effects of norepinephrine and adrenaline can be imitated by synephrine alkaloids, which are alpha-adrenergic agonists. However, the extent to which bitter orange and synephrine resemble adrenaline and norepinephrine in their effects on the cardiovascular and central neurological systems (e.g., elevated blood pressure and heart rate) remains unclear. Research has indicated that bitter orange functions as a mild appetite suppressant and promotes lipolysis and energy expenditure [8].

African mango (*Irvingia gabonensis*) seed kernel extract has been suggested to aid in weight loss through suppressing adipogenesis based on in vitro evidence. Furthermore, *I. gabonensis* proprietary extract IGOB131 lowers serum levels of leptin, a hormone that

has a positive correlation with both body weight and percentage of body fat. Low-density lipoprotein (LDL) and total cholesterol levels may also be lowered by IGOB131 [9].

Capsaicin and other capsinoids—compounds present in chili peppers—have been suggested to have anti-obesity effects due to their capacity to boost lipid oxidation and energy expenditure, decrease the postprandial insulin response, boost satiety, and decrease appetite and energy intake. Some studies have indicated that, instead of releasing satiety hormones, capsaicin increases satiety by causing gastrointestinal distress (pain, burning sensation, nausea, and bloating, for example), which may overall decrease the desire to eat [10].

Glucomannan is a natural, water-soluble dietary fiber derived from the root of the konjac plant (*Amorphophallus konjac*) that reduces the time it takes for food to pass through the digestive system, making consumers feel full. It is often used as a supplement for weight loss, digestive health, and blood sugar control due to its ability to absorb water and expand in the stomach, promoting a feeling of fullness. Glucomannan ends up in the colon undecomposed, as digestive enzymes do not act on it. It helps to maintain normal blood cholesterol and triglyceride levels. It is a very powerful ally in weight loss, as it is very low in calories and reduces the need to eat [11].

Ananas is the botanical genus that includes the pineapple (*Ananas comosus*), a tropical fruit that contains bromelain, an enzyme that helps to break down protein, can reduce bloating, and reduces the excess water from the body while having an energy content of about 50 kcal per 100 g, making it suitable for diets. Vitamin C and certain enzymes present in these fruits may also help to enhance fat burning [12].

Fucus vesiculosus, also known as bladderwrack, is a type of brown seaweed commonly found in weight loss supplements due to its high iodine content and potential metabolism-boosting properties. By stimulating thyroid activity, it may help to increase calorie expenditure and can promote satiety and reduce food intake due to its fiber content (alginate). It can also act as a mild laxative, supporting gut health and detoxification, and may help to reduce inflammation and support overall metabolic health [13].

Most of these supplements are labeled as “purely natural products”. Patients associate this labeling with the higher safety of using such products compared to drugs, but the truth is that the risks and adverse reactions are major. Illicit substances or synthetic products are often added to weight loss supplements—usually undeclared—with the intention of increasing efficacy and profit. The adulterating substances are most often of the anorectic type (e.g., sibutramine, diethylpropion/amfepramone, or phentermine), but can also be of the stimulant (e.g., ephedrine or caffeine), anxiolytic (e.g., diazepam), or antidepressant (e.g., fluoxetine) types. Benzodiazepines have been reported to be used as a masking agent in products containing anorectics, in order to mitigate their adverse side effects [14]. Most adulterating substances are classified as withdrawn from the market or prescription drugs (e.g., sibutramine and orlistat). Another substance that is used in the adulteration of herbal weight loss supplements is the laxative phenolphthalein—a substance that was withdrawn by the Food and Drug Administration (FDA) in 1997 due to its potential carcinogenic properties [15].

Adulteration of dietary supplements is a major problem putting consumers at risk. The hypothesis of the study was that some of the weight loss supplements currently marketed in European Union countries are adulterated and may present health risks despite the misleading perception of safety among consumers. Therefore, the aim of this study consists in analyzing some weight loss supplements advertised as ‘natural’ remedies, purchased from internet sites or from European specialized stores, in order to detect possible adulterants. A survey of the literature revealed numerous analytical techniques employed as detection methods, including GC–MS (gas chromatography–mass spectrometry), LC–MS (liquid

chromatography–mass spectrometry), NMR (nuclear magnetic resonance), FTIR (Fourier transform infrared spectroscopy), LC–HR-MS (liquid chromatography–high-resolution mass spectrometry), UHPLC–TOF-MS (ultra-high-performance liquid chromatography–time of flight–mass spectrometry), IMS (ion mobility spectroscopy), and CE (capillary electrophoresis) [16–23]. These analytical techniques provide precise and accurate analyses, with low detection and quantification limits, but require expensive and less accessible equipment, high-purity solvents, and qualified personnel. Therefore, they are less suitable as screening methods. On the other hand, TLC–densitometry has the advantages of ease of use, high accuracy, a low limit of detection, and being a low-cost procedure [24]. Therefore, our study proposes a new, cost-effective high-performance thin-layer chromatography (HPTLC) as a screening method to detect the adulterants in herbal dietary supplements promoted for weigh loss. This method can be successfully used to analyze samples of herbal products and supplements, both qualitatively and quantitatively, while a GC–MS method is applied for confirmation. The detection and quantification of phenolphthalein were carried out using an HPLC method.

2. Materials and Methods

2.1. Herbal Supplements

Thirty-four samples of herbal dietary supplements (hard capsules, tablets, or sachets with powder for oral suspension) were purchased from the internet or from specialized stores. The selection was based on the specified composition and on the degree of satisfaction declared by users, as determined by the review score. The samples were coded with numbers from 1 to 34, and their source, dosage form, composition, and price are detailed in Table 1.

Table 1. Characterization of dietary supplements and results of qualitative analysis.

Product Sample No./ Dosage Form	Origin	Price (EUR/Unit Dose)	Dosage (Unit Doses/Day)	Composition	Results/ Compound Identified
1/ hard capsules	China	0.36	1	Nuca koncing (*Juglans regia*), *Garcinia cambogia*, glucomannan, *Actinida chinensis*, green apple (malic acid), *Helianthus tuberosus*, cellulose from *Discorea esculenta* (12%)	NDA
2/ hard capsules	EU	0.42	2	*Rosa canina*, zeolith, *Paullinia cupana*, glucomannan, *Camelia sinensis*, *Garcinia cambogia*	Caffeine
3/ hard capsules	EU	0.43	1	Kombucha vinegar, apple pectin, *Laminaria japonica*, *Camellia sinensis*, *Fucus vesiculosus*, *Sambucus nigra*, *Citrus aurantium*, *Juglans regia*	Caffeine Phenolphthalein
4/ hard capsules	EU	1.1	2	*Malus domestica*, *Heliantus tuberosus*, *Actinidia deliciosa*, *Garcinia cambogia*, *Juglans regia*, soluble fibers (Nutriose)	NDA
5/ hard capsules	USA	0.49	3	*Garcinia cambogia* (60% hydroxycitric acid—HCA)	NDA
6/ hard capsules	EU	0.66	2	*Camellia sinensis*, *Coffea arabica*, *Garcinia cambogia*, *Paullinia cupana*, *Rubus idaeus*, *Olea europaea*, *Ananas comosus*, *Amorphophallus konjac* (80% glucomannan)	Caffeine Phenolphthalein
7/ hard capsules	Romania	0.60	2	*Garcinia cambogia*, *Camellia sinensis*, *Paullinia cupana*, *Rubus idaeus*, *Ananas comosus*, apple pectin	Caffeine
8/ hard capsules	Poland	0.22	3	L-carnitine, L-thyrosine, *Camellia sinensis*, *Garcinia cambodgia*, caffeine, *Irvingia gabonensis*, *Zingiber officinale*, *Panax ginseng*, *Piper nigrum*, chromium picolinate	Caffeine

Table 1. *Cont.*

Product Sample No./ Dosage Form	Origin	Price (EUR/Unit Dose)	Dosage (Unit Doses/Day)	Composition	Results/ Compound Identified
9/hard capsules	Romania	0.08	3–4	*Rhamnus frangula*, *Cassia angustifolia*, *Arctium lappa*, *Garcinia cambogia*, *Gymnema sylvestris*, *Equisetum arvense*, *Cynara scolymus*, *Olea europaea*	NDA
10/hard capsules	EU	0.33	2	*Coffea arabica*, *Camellia sinensis*, *Plantago ovata*, *Garcinia cambogia*, *Salix alba*, *Ananas comosus*, *Carica papaya*, *Ilex paraguarien*, *Fucus vesiculos*, *Withania somnifera*	Caffeine
11/hard capsules	Poland	0.66	2	*Zingiber officinale*, *Coffea arabica*, *Camellia sinensis*, *Irvingia gabonensis*, *Panax ginseng*	Caffeine
12/hard capsules	UK	0.20	2	Chili extract, caffeine, *Camellia sinensis*, L-carnitine, *Piper nigrum*, chromium picolinate	Caffeine
13/hard capsules	Romania	0.37	1–2 × 3–4	*Amorphophallus konjac*	NDA
14/hard capsules	Slovenia	0.20	3	L-carnitine, caffeine, L-tyrosine, green tea, *Garcinia cambogia*, Cayenne chili extract, chromium picolinate, B complex vitamins, *Piper nigrum*	Caffeine
15/hard capsules	Poland	0.18	1	*Garcinia cambogia*, vitamin C, chromium picolinate, niacin	NDA
16/hard capsules	The Netherlands	0.50	1–2 × 3	Soluble fiber derived from natural plants, *Oleum Helianthus*, *Amylum solani*	NDA
17/hard capsules	Slovenia	0.65	1	Sicilian red oranges, *Camellia sinensis*, Cayenne pepper extract, vitamin B6, *Piper nigrum*	Caffeine Phenolphthalein
18/hard capsules	EU	0.20	2	*Coffea arabica*, *Rubus idaeus*, Reishi mushrooms	Caffeine
19/hard capsules	China	0.40	2	Balsam pear, *Garcinia cambogia*, *Aloe vera*, *Cinnamomum verum*, *Crataegus monogyna*, *Nymphaea caerulea*	Caffeine Phenolphthalein
20/hard capsules	USA	0.36	1–2	Acetyl L-carnitine hydrochloridum, green tea, theobromine, L-theanine, caffeine, chromium picolinate	Caffeine
21/tablets	China	1.52	1	*Mangifera indica* fruit, *Rubus idaeus* fruit, *Momordica charantia*, *Garcinia cambogia*, *Cynara scolymus*, *Cassia angustifolia*	Sibutramine
22/hard capsules	Spain	0.27	2 × 4	*Garum armonicum*, L-taurine, stridium extract	NDA
23/hard capsules	Spain	0.23	4	*Opuntia ficus-indica*, papaya	NDA
24/hard capsules	China	1.00	1	*Citrus aurantium*, *Nelumbo nucifera*, *Cassia angustifolia*, *Alisma orientale*, L-carnitine	Sibutramine
25/hard capsules	Romania	0.18	1–2	Choline, milk thistle fruit, *Curcuma longa*, black pepper, chromium picolinate	NDA
26/hard capsules	EU	0.08	2	L-carnitine, *Camellia sinensis*, *Cinnamomum verum*, *Opuntia ficus-indica*, *Amorphophallus konjac*, *Garcinia cambogia*, chromium	Caffeine
27/hard capsules	Japan	1.4	1	Biotin, pantothenic acid, Cayenne pepper powder, *Camellia sinensis*, caffeine, carnitine, choline, *Citrus aurantium* extract, *Theobroma cacao*, *Commiphora mukul*, alpha lipoic acid	Sibutramine
28/tablets	Romania	0.13	2 × 2	*Garcinia cambogia* (60% hydroxycitric acid), *Camellia sinensis*, *Paullinia cupana* (16% caffeine), *Cynara scolymus* (2.5% cynarine), *Cinnamomum verum* (20% polyphenols), *Ananas comosus* (extract 12:1)	Caffeine
29/tablets	Romania	0.20	2	*Garcinia cambogia*, *Taraxacum officinalis*, *Ananas comosus*	NDA
30/tablets	Italy	0.18	3 × 2	Natural complex of polysaccharide macromolecules from cellulose fibers, *Opuntia ficus-indica*, glucomannan, mucilage of *Althaea officinalis*, *Tilia*, *Linum*	NDA
31/tablets	Germany	0.32	2 × 2	Active fiber polyglucosamine from shells of crustaceans	NDA

Table 1. *Cont.*

Product Sample No./ Dosage Form	Origin	Price (EUR/Unit Dose)	Dosage (Unit Doses/Day)	Composition	Results/ Compound Identified
32/powder for oral solution	EU	1.71	1	L-carnitine, *Paullinia cupana*, yerba mate tea extract, *Acacia* gum, niacin	Caffeine
33/powder for oral solution	EU	2.00	1	Fig extract powder, Java tea extract, *Galium verum*, *Cynara scolymus*, *Taraxacum officinale*, *Urtica dioica*, grape pomace extract, *Acacia* gum	NDA
34/powder for oral solution	EU	1.52	1	*Garcinia cambogia*, carobs extract, *Cichorium intybus*, choline, *Melissa officinalis*, vitamin C, vitamin B6, *Acacia* gum	NDA

EU = European Union; NDA = no detected adulterant.

2.2. HPTLC Analysis

The following standards were used: Caffeine (≥99%, Sigma-Aldrich, Saint Louis, MO, USA), phenolphthalein (≥99.9%, Sigma-Aldrich, USA), fluoxetine hydrochloride (≥98%, Sigma-Aldrich, USA), diethylpropion hydrochloride (1 mg/mL solution, Sigma-Aldrich, USA), and DL-ephedrine hydrochloride (≥99%, Sigma-Aldrich, USA). The standard stock solutions (1.3 mg/mL) were prepared using LC-grade methanol (99.9%, Merck, Darmstadt, Germany). Working solutions of various concentrations were prepared via dilution in the same solvent and were used for the qualitative analysis and to obtain the calibration curve.

Solvents: methanol (LC-grade, 99.9%), ethyl acetate (99.5%), ammonia solution 25%, toluene (≥99.5%), and formic acid (98–100%) were purchased from Merck, Germany.

Chromatographic parameters:

Chromatography was performed on pre-coated silica gel F254 glass plates (size 20.0 × 20.0 cm^2) obtained from Merck, Germany. The plates were used without any pretreatment; a Linomat 5 (Camag, Muttenz, Switzerland) equipped with a 100 µL syringe (Hamilton, Switzerland) was used for semi-automatic sample application (lines with dimensions of approx. 6–7 mm). Linomat 5 application parameters were as follows: inert gas nitrogen (as spray gas), methanol (as sample solvent), 150 nL/s (dosage speed), and a predosage volume of 0.2 µL.

The mobile phase used was ethyl acetate/toluene/methanol/ammonia at a volume ratio of 50:30:20:0.5. The distance from the lower edge was 20 mm, the distance from the side was 15 mm, and the track distance was 11.4 mm.

Ascending development was performed in a twin-trough chamber (for 20 × 20 cm^2 plates) (Camag, Switzerland) after at least 30 min of saturation; the mobile phase migration distance in all experiments was 10 cm. The densitometric scanning of obtained spots was performed using a TLC scanner 3 (Camag, Switzerland) operating in the absorbance mode and controlled with WinCATS software Version 1.4.4 (Camag, Switzerland). Deuterium and wolfram lamps were used as a radiation source. The chromatographic plates were scanned with the slit dimensions of 4.00 × 0.30 mm^2 and a scanning speed of 20 mm/s. Densitometric analysis of chromatograms was performed at 254 nm. Additional analysis was performed at the wavelength of 275 nm. The data resolution speed was 100 µm/step.

2.3. GC–MS Analysis

Equipment: A Focus gas chromatograph coupled with a DSQII mass spectrometer (Thermo Electron Corporation, Waltham, MA, USA) operating with a quadrupole and electron ionization (EI) ion source (Thermo Electron Corporation, Waltham, MA, USA) was used. A TR-5MS (stationary phase 5% phenyl polysilphenylene siloxane) capillary column (30 m × 0.25 mm × 0.25 µm film thickness) (Thermo Fischer Scientific, Waltham, MA, USA) was used for the analysis of samples. Specialized Xcalibur ver. 1.2 software

(Thermo Electron Corporation, USA) with the NIST 02 mass spectra library was used for data collection and processing.

Chromatographic separation: The determination was performed with the following temperature program: an initial temperature of 100 °C was held constant for 1 min; then, it was increased to 210 °C at a rate of 40 °C/min, and then increased to 225 °C at a rate of 5 °C/min. The third ramp was an increase to 250 °C at a rate of 30 °C/min, and the last ramp to 300 °C at a rate of 40 °C/min. The temperature was held constant at 300 °C for 2 min. The carrier gas (helium) flow rate was set to 2 mL/min. The total time of analysis was 11 min. The samples (in LC-grade methanol, 99.9%, Merck, Germany) were injected with a volume of 1 µL.

Mass spectrometer conditions: solvent elution time: 2.4 min, mass range: 10–500 a.m.u., injector temperature: 280 °C; work in split mode; transfer line temperature: 280 °C; ionization source temperature: 230 °C. The full scan mode was used for acquisition.

2.4. HPLC Analysis of Phenolphthalein

An LC 300 HPLC system (Perkin Elmer, Waltham, MA, USA) was used for analysis. Chromatographic separation was achieved using an SPP C18 Column (150 × 3.0 mm^2, 2.7 µm) (Perkin Elmer, USA) heated at 30 °C. The mobile phase consisted of formic acid in ultrapure water 0.1% (A) and formic acid in methanol 0.1% (B). A 16-min gradient was used at a flow rate of 0.4 mL/min. The step gradient was as follows: 0 min 95% A; 0–1.0 min 95% A; 1.0–13.0 min linear gradient 5% A, 95% B; 13–16 min 5% A. The injection volume was set to 5 µL. The solutions were prepared in methanol, LC-grade (99.9%, Merck, Germany). PDA detection was performed at 230 nm.

2.5. Sample Preparation/Extraction

The herbal supplement samples were presented as hard capsules, tablets, or sachets with powder for oral suspension. The tablets were ground before extraction. The extraction of the content of one unit dose was performed with 10 mL methanol (LC-grade) via sonication (using an Ultrasonic bath Elmasonic S 60 (H), Elma Schmidbauer GmbH, Singen, Germany) for 10 min, followed by 5 min centrifugation at 4000 rpm (using a refrigerated centrifuge, Sigma Laborzentrifugen GmbH, Osterode am Harz, Germany). The solvent selection and the extraction conditions were based on the literature reports and on the previous data obtained in our laboratory [19,25,26].

3. Results

3.1. Characterization of Analyzed Products

A total of 34 herbal products promoted as weight loss dietary supplements were analyzed for the presence of adulterating synthetic agents (Table 1). The products were acquired either online or from specialized retailers, with the selection criteria focusing on the specified composition and the satisfaction level reported by users, as reflected in their review scores. The places of origin of the products were as follows: EU (n = 10), Romania (n = 6), China (n = 4), Poland (n = 3), Spain (n = 2), USA (n = 2), Slovenia (n = 2), UK (n = 1), Japan (n = 1), The Netherlands (n = 1), Germany (n = 1), and Italy (n = 1). According to the labels, all products were natural, consisting of different herbal mixtures, including green tea (38.28%, 13/34 supplements), green coffee (11.76%, 4/34 supplements), guarana (14.7%, 5/34 supplements), or *Garcinia cambogia* (50%, 17/34 supplements). The price ranged from EUR 0.08 to 2.0 per unit dose. Most products were formulated as capsules (26 supplements); however, five products were formulated as tablets, and three as sachets with powder for oral suspension.

3.2. HPTLC, HPLC, and GC–MS Analysis

In the first step of the experiments, we used standard solutions to perform a series of tests to select the optimal solvent development system to separate the analytes. Different mixtures of organic solvents in various volume compositions and silica gel 60 F 254 pre-coated plates were used.

Initially, a mixture of ethyl acetate/methanol/ammonia at a volume ratio of 85:10:5 was used as the mobile phase. Standard solutions of several synthetic adulterants reported in the literature were used for qualitative analysis: phenolphthalein, fluoxetine hydrochloride, diethylpropion hydrochloride, ephedrine hydrochloride, and furosemide. A standard solution of caffeine was also applied, as many supplements have plants that contain caffeine in their declared composition. The detection of spots was performed at a wavelength of 254 nm. The results showed that this mobile phase did not adequately separate caffeine from phenolphthalein, as their Rf values were similar (caffeine = 0.78 and phenolphthalein = 0.81). Finally, a mobile phase consisting of a mixture of ethyl acetate/toluene/methanol/ammonia at a volume ratio of 50:30:20:0.5 was selected, as the best separation of the compounds was obtained (Rf caffeine = 0.65 and Rf phenolphthalein = 0.83).

The UV spectra highlighted the following maximum absorption wavelengths: 275 nm for caffeine, 236 nm for phenolphthalein, 254 nm for diethylpropion, 229 nm for fluoxetine, 211 nm for ephedrine, and 279 nm for furosemide. The UV spectra were compared to the specific spectra reported in the literature for each compound.

The results suggest high levels of caffeine in most herbal products. Therefore, a semiquantitative analysis was performed for caffeine. The calibration curve of caffeine was linear in the concentration range of 2.6–13.0 μg/spot (2.6 μg/spot; 5.2 μg/spot; 7.8 μg/spot; 10.4 μg/spot; and 13 μg/spot), using both the area and the peak height as a quantification measure ($r > 0.99$).

The specificity of the method was confirmed by comparing the Rf values and the in situ UV spectra of the samples and the standard spots of caffeine. The spectra show there is no interference and the proposed HPTLC method is specific and suitable for the determination of caffeine in tested herbal supplements. The peak purity index was above 0.999 (between 0.999723 and 0.999999), suggesting that caffeine was successfully detected under the experimental conditions.

The accuracy of the method determined based on the recovery rates (%R) and the precision (as the coefficient of variation) was evaluated using the standard addition method at three concentration levels (80%, 100%, and 120%). The accuracy ranged from 92.43% to 100.52%, while the precision ranged from 0.72% to 1.86%. These results are in the acceptable range of 1–5% for CV values in TLC densitometry [27].

A summary with various details regarding dosage form, origin (country), price, qualitative composition, and posology according to labeling, as well as the results regarding the presence of adulterants in each analyzed product, is presented in Table 1. The results indicate the presence of caffeine in 47% (16/34) of herbal supplements (Table 1, Figures 1 and 2). The presence of caffeine in all products except for S19 was correlated with the composition, as caffeine originated from natural sources (green tea, green coffee, and guarana) or was used as ingredient in the supplement (S12, S14, and S20). The products with added caffeine also contain vegetal products with caffeine such as green tea. The presence of caffeine was confirmed with the in situ UV spectra, showing an absorption maximum at 275 nm. The superposition of the UV spectra for caffeine in the standard solution and that in the analyzed sample was observed, thus contributing to the reliable identification of caffeine (Figure 2).

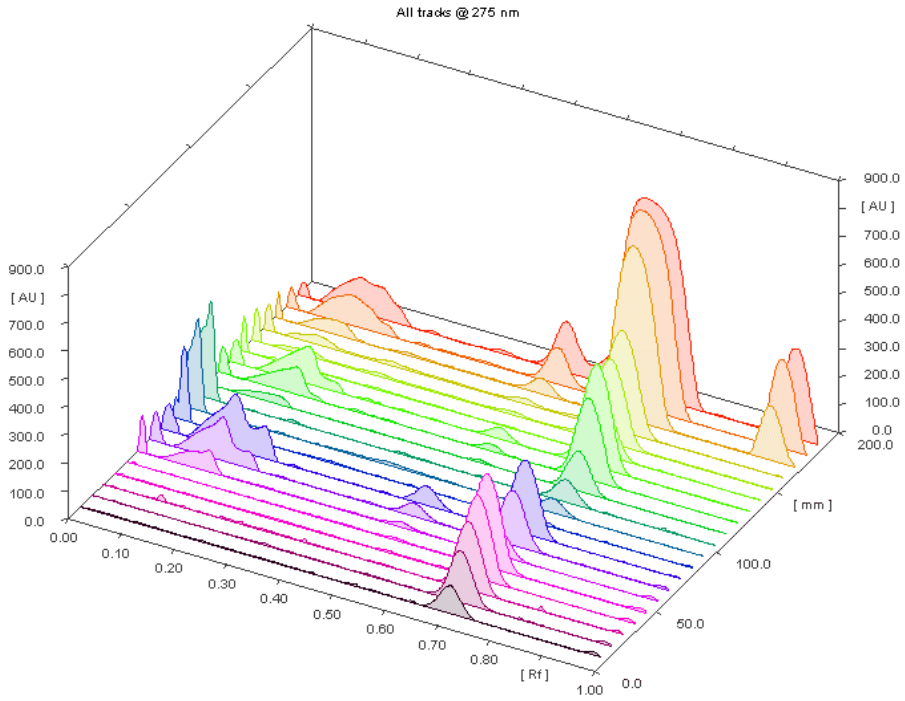


Figure 1. Three-dimensional chromatogram for caffeine (standard-track 1–5) and samples 2 (track 6–8), 3 (track 9–11), 6 (track 12–14), 7 (track 15–17), and 8 (track 18–20) (detection at λ = 275 nm; samples were applied at three concentration levels).

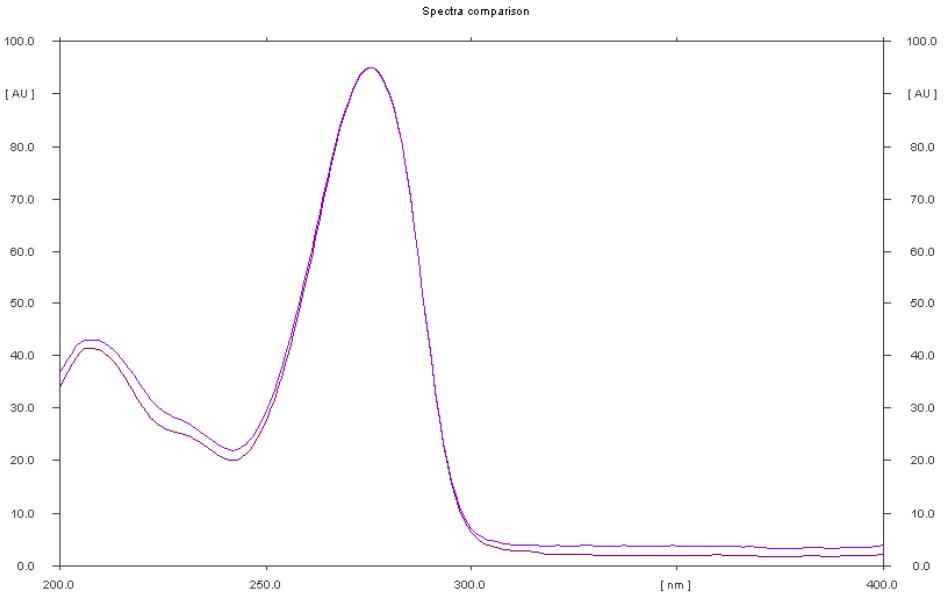
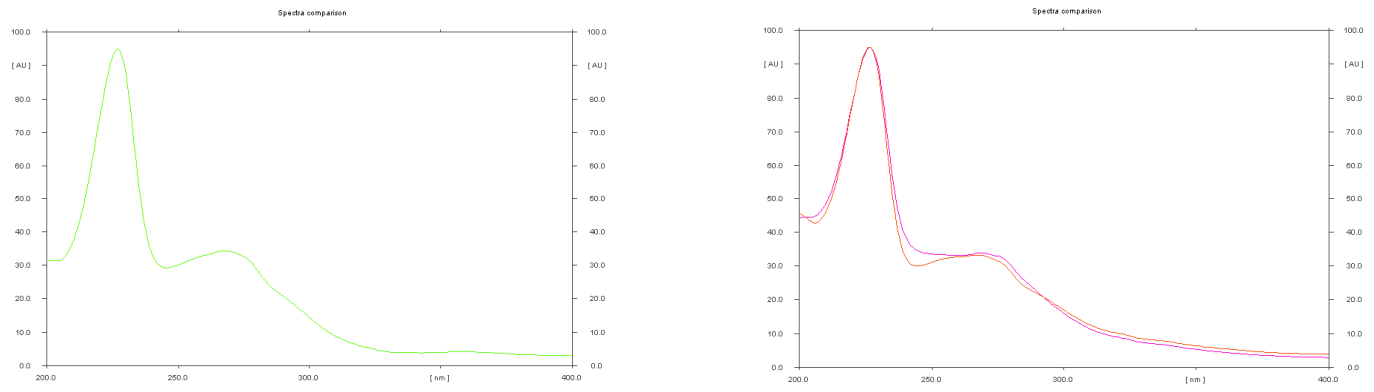


Figure 2. In situ absorbance–reflectance UV spectra of caffeine standard (violet) and sample 7 (red).

Three supplements (S21, S24, and S27) were demonstrated to be adulterated with sibutramine. In the absence of the standard, sibutramine was determined on the basis of the comparison of the in situ UV spectrum with that reported in the literature. Sibutramine's spectrum aligned with the literature findings and showed a primary absorption maximum at approximately 227 nm. Additionally, the UV spectra of all three samples showed similarity, and identical Rf values were recorded for sibutramine in these supplements. Figure 3a,b presents the in situ absorbance–reflectance UV spectra of sibutramine obtained for the three samples.



(**a**) (**b**)

Figure 3. In situ absorbance–reflectance UV spectra of sibutramine in samples S21 (**a**), S24 (red), and S27 (violet) (**b**).

The presence of sibutramine was also suggested by a rapid screening test of precipitation with ammonium reineckate detection reagent [28]. The positive test was indicated by a pink precipitate. The results were confirmed with GC–MS. The base peak of sibutramine is at m/z = 114.0 (Figure 4).

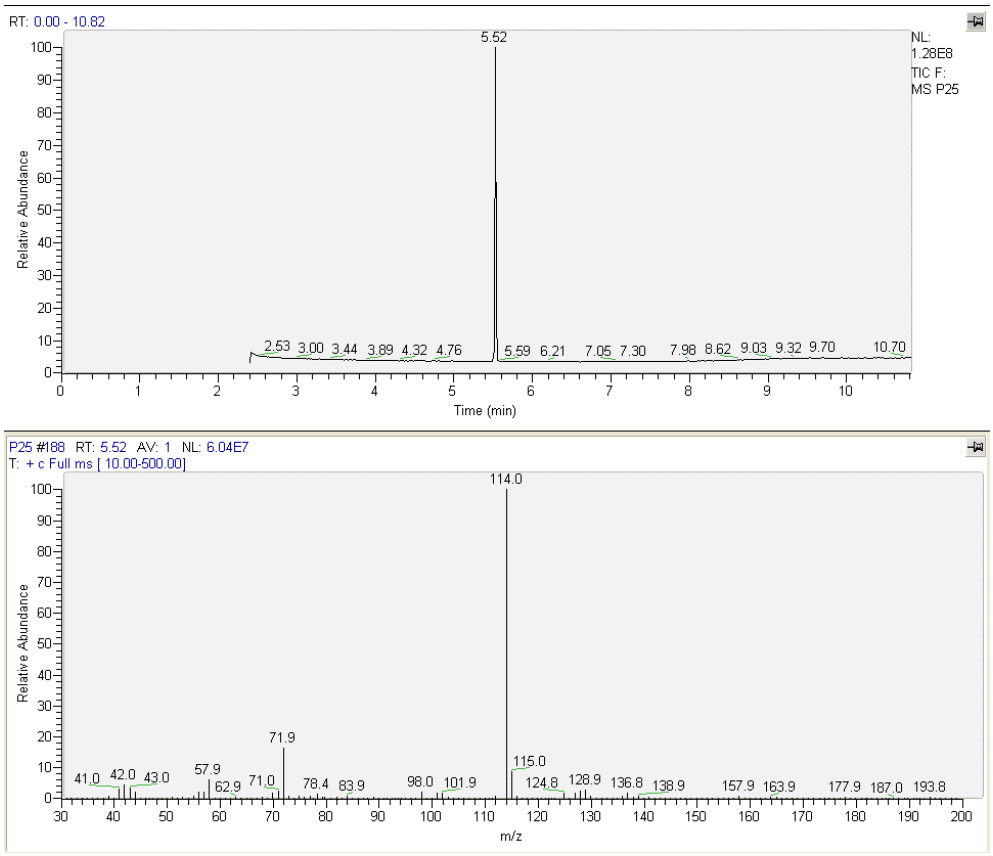


Figure 4. Chromatogram and MS spectrum for sibutramine (sample S25, Rt = 5.52 min, m/z = 114).

Fluoxetine, diethylpropion, ephedrine, and furosemide were not detected in the samples, as indicated by the Rf values and the UV spectral analysis. In four samples (S3, S6, S17, and S19), phenolphthalein was detected using an HPLC method with diode-array detection (Figure 5).

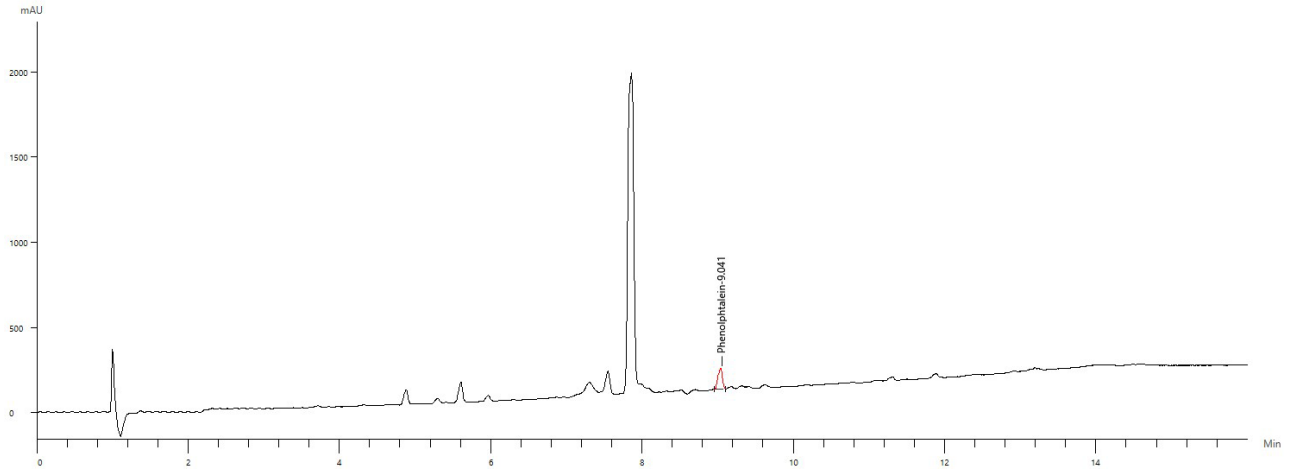


Figure 5. Chromatogram for phenolphthalein (sample S3, Rt = 9.041 min).

Given that most of the supplements contain one or more vegetal products with caffeine and some supplements have caffeine added as a separate ingredient, the amount of caffeine was evaluated using the HPTLC method. The quantity of caffeine ranged from 2.5 to 302 mg/unit dose. The high concentrations were obtained in the supplements with added caffeine (S12, S14, and S20). The quantity of caffeine determined exceeded the amount on the label for S14 and S20 (178% of the declared amount in S14 and 200% in S20). The quantity of the added caffeine was not declared for the S14 supplement.

The quantity of phenolphthalein was also determined via HPLC in supplements S3, S6, S10, and S12 (Table 2). The method range was 2.5–15.0 μg/mL (2.5 μg/mL; 5.0 μg/mL; 7.5 μg/mL; 12.5 μg/mL; and 15.0 μg/mL). The amount ranged from 104 to 293 microg/unit dose.

Table 2. Quantitative analysis of caffeine and phenolphthalein in dietary supplements.

Product Sample No./ Dosage Form	Quantity of Caffeine (mg/Unit Dose)	Quantity of Phenolphthalein (μg/Unit Dose)
2/hard capsules	10.41	-
3/hard capsules	2.53	-
6/hard capsules	19.00	293.2
7/hard capsules	22.39	-
8/hard capsules	70.3	-
10/hard capsules	9.37	175.9
11/hard capsules	41.80	-
12/hard capsules	124.70	-
14/hard capsules	143.00	-
17/hard capsules	6.15	107.10
18/hard capsules	98.90	-
19/hard capsules	3.41	104.70
20/hard capsules	301.6	-
22/hard capsules	5.43	-
23/hard capsules	124.70	-
26/hard capsules	143.00	-
28/tablets	ND	-
32/powder for oral solution	ND	-

ND = not determined.

4. Discussion

At present, obesity is becoming a serious problem, as it has been shown that this pathology has reached alarming rates around the world. Fast food consumption and lack of physical activity contribute significantly to the development of obesity. Therefore, herbal

supplements for weight loss have increased in popularity, use, and availability. These products are very popular, as they are promoted as being natural and safe.

Adulterated dietary products, including supplements for weight control, are a global problem that poses health risks to those who consume them. The composition of the products is based only on the manufacturer's own declaration, which is listed on the packaging. Moreover, manufacturers are responsible for ensuring that the supplement is safe, as the safety of the product is not evaluated before marketing. In this context, the analysis of dietary supplements in order to detect possible adulteration with synthetic chemicals is very important.

It has been shown that many weight loss supplements are contaminated with synthetic chemicals not specified on the label. The most common classes of adulterants are anorectics (sibutramine amfepramone), stimulants (caffeine, ephedrine, synephrine), antidepressants (fluoxetine), diuretics, and laxatives (such as phenolphthalein). These chemical compounds could be responsible for a series of serious adverse reactions in consumers; therefore, the adulteration of dietary supplements has become an important problem worldwide.

The current study involved the analysis of a selection of herbal supplements marketed for weight reduction in order to detect possible adulterants. A total of 34 products purchased from the internet or from EU specialized stores were studied using a new HPTLC method for adulterant screening. TLC and HPTLC techniques have been reported to be useful, simple, and economic methods for the routine analysis of illegally added anorectics (e.g., sibutramine) and phosphodiesterase inhibitors in different herbal supplements [26,29,30].

We confirmed the presence of identified adulterants by a GC–MS technique, while HPLC with a diode array detector was employed for the qualitative and quantitative analysis of phenolphthalein. The HPTLC method is efficient, rapid, and cost-effective, making it suitable for use in small laboratories to monitor adulteration in herbal supplements. Although TLC methods typically have lower selectivity and sensitivity compared to GC–MS and HPLC techniques, these limitations can be mitigated by choosing an appropriate detection approach for analysis. Utilizing HPTLC with densitometry and UV spectral analysis significantly enhances accuracy and precision, enabling more reliable and precise identification results.

Various pharmaceutical dosage forms were studied. While the origins of the products were diverse, the declaration was imprecise for most supplements, with the labels stating that they were manufactured in the EU.

Our results indicate that caffeine is present in most analyzed supplements (47%). These results are expected, as many supplements have natural sources of caffeine in their composition, such as green tea, guarana, green coffee beans, or cocoa. In some products, caffeine is added and declared on the label, but not all products indicate the caffeine amount.

Caffeine (1,3,7-trimethylpurine-2,6-dione, part of the purine group) is one of the most common CNS stimulants. These substances work by controlling certain neurotransmitters, such as serotonin. Serotonin supplementation produces minimal weight loss, despite the results of scientific experiments. For some, this small weight loss is sufficient due to the psychological as well as physical impacts; however, for others, the risks outweigh the benefits. For example, CNS stimulants increase blood pressure and heart rate and, so, are not recommended for patients with heart disease or high blood pressure. While experimental evidence regarding the sympathomimetic effect of caffeine as a strong inhibitor of cyclic adenosine monophosphate phosphodiesterase (cAMP) is extensive, a sufficient concentration for this inhibition to occur is not reached in humans. Caffeine inhibits phosphodiesterase enzymes in skeletal muscle and adipose tissues with the consequence of an increase in the intracellular concentrations of cAMP. This results in the promotion of lipolysis via the activation of hormone-sensitive lipases with the release of

free fatty acids and glycerol. An increase in thermogenesis in a dose-dependent manner is also highlighted [31,32].

Caffeine has been found to influence the energy balance by increasing energy expenditure (EE) and decreasing energy intake (EI); therefore, it can potentially be useful as a body weight regulator since obesity is caused by an imbalance between EI and EE [33].

Recent data suggest that adults maintain their weight if they consume significantly more cups of coffee and caffeinated beverages after losing extra pounds than the general population, so caffeine may help to maintain weight loss. Higher coffee consumption was associated with a lower risk of obesity, metabolic syndrome, and type 2 diabetes, suggesting prevention of obesity through coffee consumption. However, clinical studies investigating the effects of caffeine on body weight are lacking, and further research is needed to confirm these findings. The FDA, the European Food Safety Authority (EFSA), and the American Medical Association (AMA) recommend that adults consume no more than 400–500 mg/day of caffeine. Doses of 15 mg/kg can be toxic to an adult and can cause nausea, vomiting, tachycardia, convulsions, and cerebral edema, and combinations of caffeine with other stimulants such as bitter orange can potentiate these effects. Concomitant administration of caffeine with other drugs metabolized by CYP1A2, including selective serotonin reuptake inhibitors, antiarrhythmics, MAOIs, lithium, bronchodilators, and quinolones, may lead to drug interactions with toxic effects [34].

The composition of herbal dietary supplements on the market varies significantly in both quality and quantity, depending on the manufacturer. Many of these supplements often include caffeine-containing plants, such as green tea, green coffee, or guarana. However, there are currently no regulations in place to standardize caffeine content.

As per the labeling, only three out of 34 products (S12, S14, and S20) contain caffeine added as separate ingredient. However, the specific amount of added caffeine in the S14 supplement is not disclosed. Furthermore, 31 out of 34 products contain caffeine from herbal sources, but the amount per unit dose is not provided. These explain the significant difference between the minimum and maximum caffeine levels. For S14 and S20, the measured caffeine content significantly exceeded the labeled values, which may be considered as adulteration. This could result in side effects, considering the recommended supplement dosage (1–2 capsules/day for S20 and one capsule $\times$3/day for S14) and the possibility of habitual daily coffee consumption. Caffeine is widely used in food through the consumption of coffee, chocolate, and fizzy beverages. The caffeine content of various fizzy or soft drinks varies between 6 mg (a cup of cocoa) and 80 mg (a cup of coffee or a dose of energizer—250 mL). Chocolate contains between 15 and 90 mg/100 g of caffeine. For most adults, a daily dose of caffeine of 400 mg is considered safe [35–37]. However, there is a wide variation in people's sensitivity to the effects of caffeine, and there may be interindividual differences in its pharmacokinetics. Moreover, certain pathological conditions, such as cardiovascular diseases, may result in greater sensitivity to the effects of caffeine, and there may also be pharmacodynamic interactions with some medications. Excessive caffeine consumption can cause adverse effects such as insomnia, nervousness, irritability, headache, tachycardia, frequent urination, and muscle tremors [38,39].

The studied herbal supplements frequently include green tea, guarana, bitter orange, *Garcinia cambogia*, ananas fruits and, sometimes, apple pectin, cayenne chili, or amino acids such as carnitine and tyrosine and vitamins (C and B group). Chromium picolinate is also commonly present, as it is claimed to aid weight loss via the reduction in appetite, especially the desire for sweets and sugar, despite limited scientific evidence [40,41].

It is worth noting that the recent literature data provide evidence for the hepatotoxicity potential of *G. cambogia*, either alone or in combination with green tea in herbal dietary supplements [42–44]. In the present study, there were six herbal supplements containing

G. cambogia and four supplements with the combination *G. cambogia* and green tea. The recommended dose is up to 4 unit doses/day for some products, and caution should be exercised when *G. cambogia* is used by people with liver disease or in combination with drugs or supplements with hepatotoxic potential.

Herbal diet supplements for weight control are marketed increasingly often, as they promise guaranteed weight loss and most often in a relatively short time. These products have increased adherence because patients consider them natural, without side effects. Because this category of products is not subject to rigorous controls regarding the composition and quality of the ingredients listed on the label, cases of fraudulent contamination with various dangerous substances have been reported in recent years [17,18,21,25,45].

In our study, sibutramine was detected in three of the selected supplements (S21, S24, and S27), which were classified as natural slimming products and were not labeled as containing any synthetic adulterants. According to the label, these products originate in China (S21 and S24) and Japan (S27). The S21 supplement is declared to contain fruit extracts that can contribute to weight loss. The product is claimed to be a 100% natural food supplement for weight control that significantly reduces appetite. The recommended dosage is one tablet/day, and it is not recommended to consume alcoholic, energy, or carbonated drinks or coffee. There is a labeling inconsistency regarding the pharmaceutical form, as the product is presented in tablet form while the label states that it is in capsule form.

The S24 supplement is promoted as a unique formula based on natural and safe ingredients that was designed to reduce appetite and accelerate metabolism. The daily dose is one capsule/day, and the product is recommended for people who want to achieve fast and sustainable results in the weight loss process. This product is frequently reported to be adulterated with sibutramine [46,47].

The third adulterated supplement, S27, is presented as natural capsules. It is declared as a completely new weight loss product (a new, improved formula of a well-known product), without analogues on the market to date. The previous formula of this supplement also has a history of reports of adulteration with sibutramine [48]. The product is claimed to be a magic slimming pill that reduces appetite, improves and accelerates metabolism, blocks the accumulation of new fat deposits, and breaks down those already stored by the body. A loss of 7 to 12 kg per month is claimed. The patient leaflet mentions possible side effects such as increased thirst and sweating, mild headaches, temporary side effects such as insomnia, nervousness, increased heart rate, and dizziness. It is worth mentioning that common side effects of sibutramine include dry mouth, headache, insomnia, constipation, nausea, and increased blood pressure and heart rate. The S27 product also contains added caffeine (65 mg/capsule). When combined, sibutramine and caffeine may have additive stimulant effects and potentially increase the risk of cardiovascular problems.

Sibutramine, or 1-[1-(4-chlorophenyl)cyclobutyl]-N,N,3-trimethylbutan-1-amine, is an anorectic agent that was approved as an obesity medication by the Food and Drug Administration (FDA) in 1997 (Meridia, manufactured by Abbott Laboratories) and by the European Medicines Agency (EMA) in 1999 (Reductil, manufactured by Abbott Laboratories). Sibutramine's action is similar to that of amphetamines, which are central nervous system stimulants and inhibit the reuptake of norepinephrine, noradrenaline, and serotonin, thus reducing appetite. Due to its side effects, especially cardiovascular events (increased blood pressure and pulse and increased risk of heart attack and stroke) and excitation of the central nervous system (nervousness, xerostomia, headache, numbness, and paresthesia), it was withdrawn from the market in January 2010 by the EMA [49] and in October 2010 by the FDA [50].

In four supplements (S3, S6, S17, and S19), phenolphthalein was detected, although in low amounts. Phenolphthalein, or 3,3-bis(4-hydroxyphenyl)-2-benzofuran-1-one, has been used for over a century as a laxative in some over-the-counter laxative products, but is now being removed after studies indicated that it is genotoxic and presents a potential carcinogenic risk [51]. The quantity of phenolphthalein ranged from 104 to 293 microg/unit dose. The results are in agreement with recent studies that reported similar amounts of phenolphthalein in herbal weight loss supplements [18].

Current studies frequently identified anorectic stimulant and laxatives as adulterants in herbal slimming supplements. Our results are consistent with the literature reports, as sibutramine and phenolphthalein were the most commonly observed adulterants in dietary slimming products [17,18,48,52]. Moreover, these findings highlight the importance of implementing stricter regulations for the introduction of herbal food supplements to the market and enhancing quality control measures. They also call for greater consumer awareness regarding the risks of using adulterated supplements and the identification of adverse reactions caused by synthetic adulterants.

5. Conclusions

An analysis of 34 herbal supplements for weight loss from the EU market was conducted using a straightforward, new HPTLC method developed to detect adulterants. The results were verified using GC–MS and HPLC analysis. Some of these supplements, predominantly imports from Asia, contained unlisted adulterants such as sibutramine and phenolphthalein, posing serious health risks.

Adulterated dietary products, particularly weight loss supplements, jeopardize consumer health also in the EU. Manufacturers are responsible for ensuring product quality, as these items are not analyzed prior to market release. Therefore, stronger regulations on product registration, marketing, and sales are urgently needed to safeguard consumer health.

In this context, healthcare providers play a crucial role in encouraging patients to maintain balanced diets and active lifestyles while highlighting the dangers of relying on such "quick fix" herbal supplements for weight loss promoted and sold online.

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Abbreviations

The following abbreviations are used in this manuscript:

AMA	American Medical Association
BMI	Body mass index
cAMP	Cyclic adenosine monophosphate phosphodiesterase
CE	Capillary electrophoresis

CNS	Central nervous system
EE	Energy expenditure
EFSA	European Food Safety Authority
EI	Energy intake
EMA	European Medicines Agency
EU	European Union
FDA	Food and Drug Administration
FTIR	Fourier transform infrared spectroscopy
GC–MS	Gas chromatography coupled with mass spectrometry
HPLC	High-performance liquid chromatography
HPTLC	High-performance thin-layer chromatography
IMS	Ion mobility spectroscopy
LC–HR-MS	Liquid chromatography–high-resolution mass spectrometry
LC–MS	Liquid chromatography–mass spectrometry
LDL	Low-density lipoprotein
MAOIs	Monoamine oxidase inhibitors
NMR	Nuclear magnetic resonance
TLC	Thin-layer chromatography
UHPLC–TOF-MS	Ultra-high-performance liquid chromatography–time of flight–mass spectrometry
WHO	World Health Organization

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