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RESEARCH ARTICLE

Exploring the Detection of Undeclared Sibutramine in Botanical Weight Loss Products, Black Slim

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ABSTRACT

Background: Currently, a significant number of individuals rely on herbal medicines for their healthcare requirements despite the lack of screening for efficacy and safety in traditional drugs. Regrettably, undeclared active pharmaceutical ingredients (APIs) have been found in traditional medicines that claim to be natural. This study aimed to identify undeclared APIs in weight loss herbal supplements obtained from an online herbal shop in Iran. **Materials and Methods:** A packet of herbal supplements consisting of 30 capsules was acquired from an online herbal store in Iran. The product is advertised as a weight loss aid. To identify any concealed APIs, a sample of the supplement was analyzed using a gas chromatography/mass spectrometry device. **Results:** Sibutramine was found in herbal supplements at a concentration of 13.43 ± 0.291 mg/capsule. **Conclusion:** Although synthetic drug production requires authorization from licensing authorities, the manufacture of herbal supplements in Iran is not regulated. Consequently, guaranteeing the quality and safety of these herbal supplements is vital for patient health.

Keywords: Adulteration, serotonin and norepinephrine reuptake inhibitor, sibutramine, weight loss supplement

INTRODUCTION

Traditional medicine, an ancient form of healthcare, is being explored for health maintenance, preventive care and diagnosis along with treatment.[1-4] Throughout history, plants have been essential resources for medicinal practices.[5] According to the World Health Organization (WHO) and some studies, majority of the world's people tend to self-prescribe herbal medicine for their primary healthcare needs without consulting a healthcare professional.[1,2,6-9] Iranians have seen a significant increase in the use of herbal medications and natural dietary supplements.[10] Many countries are adopting and expanding the coverage of traditional medicine healthcare services as an effective health resource.[5,11,12] The Ministry of Health and Medical Education of Iran has implemented good agriculture practices for herbal medications in various departments.[10] People generally consider herbal medicines are harmless, due to their natural composition, compared with orthodox medication.[13] Unfortunately, unapproved and handmade herbal medicines are not subject to periodic screening from efficacy and safety perspectives due to high costs.[14,15] Therefore, they may occasionally result in idiosyncratic or dose-related toxicity.[16] Both developing and developed countries are grappling and struggling with the threat and adverse health effects of counterfeit medicines.[17] The issue of undeclared pharmaceuticals in herbal medicines is widespread, particularly among formulations of Asian origin.[18] There are reports about counterfeit medicines in the pharmaceutical market of Iran.[19] Obesity is characterized by an excess accumulation of body fat with a body mass index ≥30 kg/m^2.[20,21]

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Obesity is a significant public health concern associated with various weight-related complications, including cancer, cardiovascular disease (CVD), hypertension, and diabetes.[22-26] It affects 32% of the global population and has reached epidemic proportions, especially among high-income groups.[24,27] Research conducted in Iran has revealed a significant prevalence of obesity and its associated complications.[28-30] There are various protocols for obesity treatment; The unified protocol, the enhanced recovery after bariatric surgery, intensive behavioral therapy, and comprehensive nutritional protocols.[31-34] Medication-assisted therapy for obesity includes the administration of certain medications such as phentermine, orlistat, and sibutramine to achieve weight loss, with sibutramine being banned due to CVD.[35-39] This study aimed to determine undeclared active pharmaceutical ingredients (API) in weight loss herbal supplements.

MATERIALS AND METHODS

Chemicals

Methanol was purchased from Merck Co. in Darmstadt, Germany. The standard for sibutramine hydrochloride monohydrate was prepared from Sigma Chemical Ltd (UK), and Helium gas (99.999% purity) was purchased from Faransanat Co. (Tehran, Iran). All chemicals and solvents were of analytical reagent grade.

Sampling and Sample Preparation

A supplement package containing 30 capsules, advertised as a weight loss supplement, was obtained from an online herbal shop in Iran (www.herbalsinaa.ir). It should be noted that the herbal shop was not registered with the Iranian Food and Drug Administration. All capsules were analyzed by forensic toxicology laboratory to detect undeclared APIs as previously described.[19,40] Briefly, organoleptic characteristics such as sample weight, odor, and color, were reported for each capsule. We used simple liquid–liquid extraction (LLE) for drug extraction as follows: One mg of sample and 3 mL of methanol were mixed for 20 min in a test tube using a rotator, then the mixture was centrifuged (3 min at 3000 rpm), and finally the supernatants were filtered with a polytetrafluoroethylene syringe filter (Macherey-Nagel, Germany) and collected. For qualitative analysis, extracted samples injected into gas chromatography-mass spectrometry (GC-MS).[41] The injection volume was equal to 0.2 µL in splitless mode.

Method Validation Procedures

Validated GC-MS techniques were used for the systematic toxicological analysis of all samples.[42] A GC (7890B model, Agilent, USA) fitted with a split/splitless injector was applied and an HP5-MS capillary column (5% phenyl silicone, and 95% dimethyl polysiloxane, 30 m length × 0.25 mm ID × 0.25 µm film thickness) was used. The GC parameters were as follows: injector temperature, 280°C; transfer line temperature 310°C; initial column oven temperature set to 80°C and held constant for 1 min. The oven temperature program rate was 10°C/min, the final temperature was set to 300°C, and the final hold was 22 min (total time: 45 min). The helium carrier gas (99.99% purity) was maintained at a constant flow rate of 1.2 mL/min.

A mass analyzer (5977B model, Quadrupole, Agilent, USA) was connected to the column and operated by electron impact (70 eV) in positive full-scan mode (50–550 m/z). The national Institute of Standards and Technology-2014, Maurer/Pfleger Weber (MPW) (MPW; 2011), and Wiley (2011) libraries were used to identify of undeclared APIs. The GC/MS method for the detection of many drugs was pre-validated in a forensic laboratory, according to my previous studies.[19,40] Sample preparation steps and instrumental conditions were set as a general method for detecting of drugs with natural, acidic, and basic structures. The linearity of the proposed method was examined by creating a calibration graph for sibutramine. The graph displays the analyte peak areas for five different concentrations (three replicates per concentration level). The obtained data were analyzed by regression analysis and fitted to the

equation y = ax + b. The method determined the limit of detection and limit of quantitation using the standard deviation (SD) of the results from 10 injections of a low concentration of sibutramine [Table 1]. Sibutramine was used as the internal standard for quantitative analysis. To calibrate the method, five-point calibrators were triplicate tested (in triplicate); 400, 800, 1600, 3200, and 6400 ng/mL. The regression line was plotted and expressed as a correlation coefficient (R_2 = 0.9990) using the least squares method to evaluate the correlation between the area under the curve and sibutramine concentration.

RESULTS

In the current study, undeclared APIs in herbal supplements were detected using the LLE extraction technique and GC-MS. Results showed that the pocket of herbal supplements has a manufacturer' name (SLIM NOIR CO) manufacture date (03/2020) and expiration date (09/2022). It does not contain product numbers, batch numbers, or ingredients. The drug labels did not disclose the presence of pharmaceutical ingredients. All red capsules had an herbal smell, white in color, no label, and the mean weight of tablets was 250.001 ± 0.261 mg (Mean ± SD) [Figures 1 and 2].

All samples were found to contain sibutramine based on the quantitative analysis results. The identification of sibutramine was confirmed using retention time (13.50 min) and spectrums (base peak is 114.1 m/z) of standards. Therefore, for identification, the analyte was confirmed by comparing the ion ratios of the unknowns to those of the standards. The quantitative analysis of the capsules showed that the sibutramine concentration was 13.43 ± 0.291 mg/capsule [Figures 3 and 4, Table 2].

The method validation results are presented in Table 1 and Figure 5.

DISCUSSION

The availability of herbal products online has made it possible for consumers to purchase herbal remedies without expert guidance; however, there are risks associated with this approach.[6,43,44] Before buying herbal medicines, it is recommended to consult with health professionals due to the lack of regulations and oversight in online herbal shops in Iran.[44-48] Various guidelines on the safe use of traditional medicines have been published by the European Medicines Agency, the WHO, and the US FDA.[49-52] Herbal medicines online may contain undeclared harmful substances.[44] The reason for adding undisclosed APIs to herbal supplements is to enhance their effectiveness for consumers.[53] According to some studies, side effects due to the adulteration of traditional medicines are associated with various adverse effects, such as cardiac arrhythmias.[15,54,55]

This research, consistent with other studies, has shown that herbal weight loss supplements may be adulterated with sibutramine.[56-58] Sibutramine, an inhibitor of serotonin and norepinephrine reuptake, has been proven effective in promoting and maintaining weight loss, especially by increasing satiety and energy expenditure.[59,60] Sibutramine is commonly found in adulterated herbal weight-loss supplements.[61] Undeclared sibutramine in herbal medicines poses serious health risks such as marginal weight loss, psychosis, hypertension, CVD, and death.[62-65] Sibutramine, an anti-obesity agent, was discontinued in numerous countries in 2010.[63,66]

Considering these findings, it is recommended that, alongside further research and study, new protocols be established for the regulated production and

Table 1: Results of method validation

Parameters	Formulae	Results (%)
Recovery percentage	100 (spiked matrix/actual concentration)	101.03
Coefficient of variation (CV%) or Relative standard deviation	100 (Standard deviation/mean)	0.6
Limit of detection	3 (SD of low concentration/slope of calibration curve)	0.04 ng/mL
Limit of quantification	10 (SD of low concentration/slope of calibration curve)	0.13 ng/mL

Table 2: Sample numbers and active pharmaceutical ingredients detected in adulterated herbal weight-loss drugs

Sample number	Dosage form	Detected active pharmaceutical ingredients	Quantity of drugs in the formulations
1	Red capsule	Sibutramine	13.56 mg/capsules
2	Red capsule	Sibutramine	13.81 mg/capsules
3	Red capsule	Sibutramine	13.51 mg/capsules
4	Red capsule	Sibutramine	13.07 mg/capsules
5	Red capsule	Sibutramine	13.32 mg/capsules
6	Red capsule	Sibutramine	13.45 mg/capsules
7	Red capsule	Sibutramine	13.06 mg/capsules
8	Red capsule	Sibutramine	13.85 mg/capsules
9	Red capsule	Sibutramine	13.00 mg/capsules
10	Red capsule	Sibutramine	13.45 mg/capsules
11	Red capsule	Sibutramine	13.38 mg/capsules
12	Red capsule	Sibutramine	13.67 mg/capsules
13	Red capsule	Sibutramine	13.83 mg/capsules
14	Red capsule	Sibutramine	13.51 mg/capsules
15	Red capsule	Sibutramine	13.46 mg/capsules
16	Red capsule	Sibutramine	12.79 mg/capsules
17	Red capsule	Sibutramine	13.35 mg/capsules
18	Red capsule	Sibutramine	13.46 mg/capsules
19	Red capsule	Sibutramine	13.15 mg/capsules
20	Red capsule	Sibutramine	13.67 mg/capsules
21	Red capsule	Sibutramine	13.64 mg/capsules
22	Red capsule	Sibutramine	13.81 mg/capsules
23	Red capsule	Sibutramine	13.07 mg/capsules
24	Red capsule	Sibutramine	13.44 mg/capsules
25	Red capsule	Sibutramine	13.12 mg/capsules
26	Red capsule	Sibutramine	13.49 mg/capsules
27	Red capsule	Sibutramine	13.62 mg/capsules
28	Red capsule	Sibutramine	13.37 mg/capsules
29	Red capsule	Sibutramine	13.04 mg/capsules
30	Red capsule	Sibutramine	13.93 mg/capsules
Mean ± SD			13.43±0.291 mg/capsules

SD: Standard deviation

Figure 1: Packaging of counterfeit herbal weight loss supplement labeled "Black Slim"

Figure 2: Counterfeit herbal weight loss tablets labeled "Black Slim" containing sibutramine

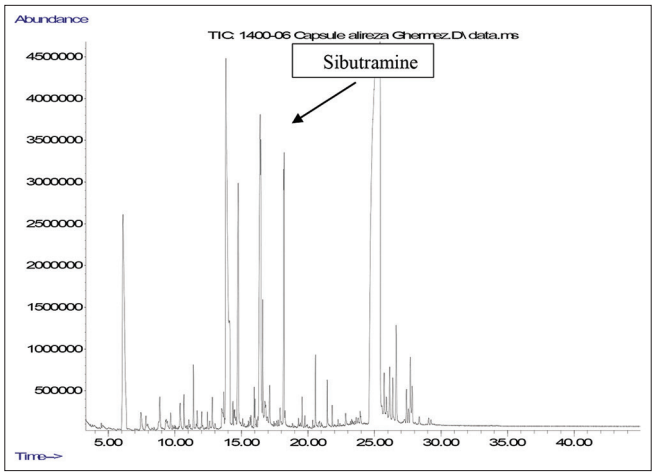

Figure 3: Gas chromatography chromatogram of sibutramine separated from adulterated herbal weight-loss drugs

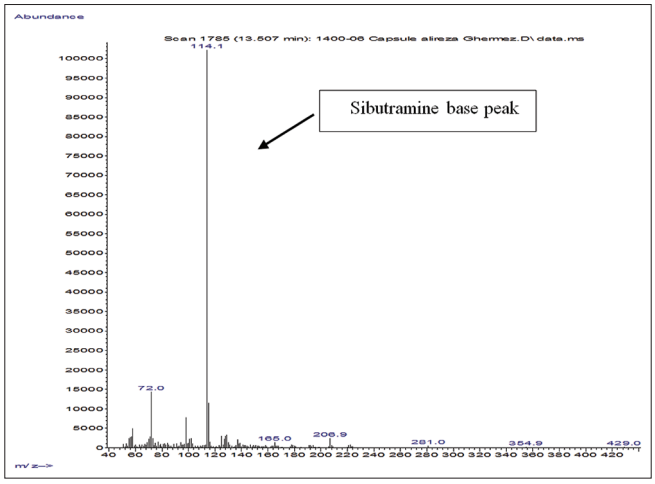

Figure 4: Mass spectrum of sibutramine separated from adultrated herbal weight-loss drugs

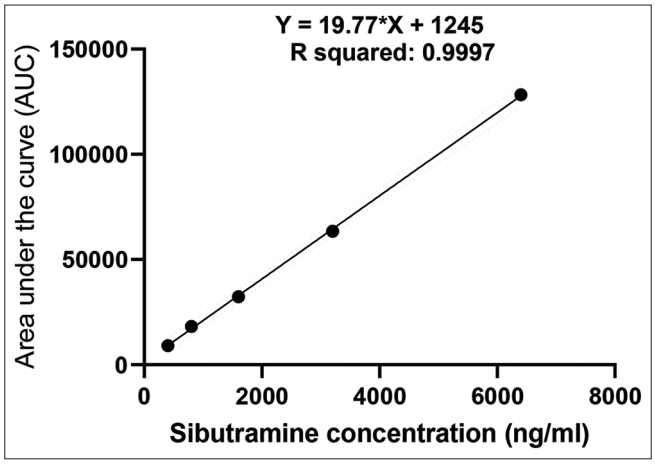

Figure 5: Linearity plots for five different concentrations of sibutramine using gas chromatography-mass spectrometry instrument

marketing of herbal drugs, as well as for the avoidance of using unapproved herbal medications.

CONCLUSION

This article highlighted the presence of undisclosed APIs in herbal weight loss supplements available in Iran. These findings indicate that these products might contain undeclared APIs. Given the lack of regulation and oversight in the production and sale of herbal drugs in Iran, it is imperative to verify the quality and safety of these natural supplements to protect patient health.

Ethical Considerations

All ethical principles were considered in this study.

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No finding.

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