

# Determining the Effective Substance of Prevalent Super Slim Weight Loss Capsule

MARYAM AKHGARI<sup>1</sup>, BAHMAN HAJ MOHAMMADI<sup>2\*</sup>, FARZANEH JOKAR<sup>1</sup>, ZAHRA MOUSAVI<sup>2</sup>

<sup>1</sup>Legal Medicine Research Center, Legal Medicine Organization, Tehran, Iran<sup>2</sup>MSC Student, Department of Toxicology & Pharmacology, Faculty of Pharmacy, Islamic Azad University (IAUPS), Tehran, Iran

<sup>2</sup>Department of Pharmacology and Toxicology, Faculty of Pharmacy and Pharmaceutical Sciences, Tehran Medical Sciences, Islamic Azad university, Tehran, Iran

## Abstract

**Introduction:** Given the growing prevalence of obesity in industrial societies including Iran, there is a growing demand for herbal weight loss drugs. Taking into account the heavy advertisements to sell the capsule as an herbal medicine, the present study was conducted in 2012 to determine the effective substance of prevalent super slim weight loss capsule.

**Methodology:** Twenty-six super slim capsules were purchased from Tehran-based pharmacies and herbal medicine shops in 2012. Afterwards, 0.5 gram of the samples was solved in 2.5ml methanol. The samples were filtered and brought up to the volume by adding 5ml of ethanol and placed in an ultrasound device for 30min. 50µl zolpidem was then added as an internal standard. From each sample, 30µl was injected into high performance liquid chromatograph at mobile phases including water, methanol, and triethylamine at volumetric ratios of (0.5+79.5+20v/v/v, pH=5.65) and the obtained peaks were analyzed after 30mins.

**Findings:** The results showed that prevalent super slim weight loss capsules found in Iran market were not herbal based and the effective substances were synthetic compounds known as sibutramine and mirtazapine. The results of quantitative analysis of the samples showed that pharmaceutical concentration of sibutramine in the capsules ranged from 33.51µg/ml to 286.78µg/ml. In addition, pharmaceutical concentration of sibutramine in the capsules ranged from 33.51µg/ml to 286.78µg/ml – pharmaceutical variables (placebo).

**Conclusion:** Despite the claims and advertisements by the producers, the drug is not herbal based and contains illicit compounds. Therefore, it is essential to improve transparency in the assessments of the damages caused by weight loss drugs.

**Keywords:** Gas Chromatography; Illicit Drugs; Mass Spectroscopy; Obesity; Weight Loss

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## INTRODUCTION

Obesity is one of the main and growing health problems in Iran (1). According to the estimates by the World Health Organization (WHO), about 1.3 billion adults in the world suffer obesity and overweight (2). Obesity is the third cause of death in the world (3) and 35% of women and 31% of men above 19 years old and 20-25% of children in the US suffer obesity or overweight (4). In its report of the non-communicable diseases, the Ministry of Health and Medical Education in Iran indicated that prevalence of overweight and obesity was 14% and 4.2% for males and 19.3 and 6.3% for females, respectively. It is notable that the problem is a growing one (5). Strategies to lose weight include diets, change of life style, behavioral techniques, and medical therapy (4-7). Along with a group of people who find exercising and healthy diet the best ways to lose weight, a group of people try to find easier and simpler solutions (8). Herbs are used worldwide for a wide variety of indications and are usually considered to be nontoxic by the general

public due to their natural origin (9-10).

As a method to treat obesity, herbal drugs sound like a reasonable solution; however, due to lack of awareness, unreliable advertisement that only seeks higher profits, and prescription of the drugs by non-expert individuals, those who use such solutions encounter several problems (11).

Nowadays, the market of weight loss pills is growing and such drugs are heavily advertised with promises of no side-effects and that “even ineffective, you have nothing to risk by taking a few herbal drugs” (12).

In reality, however, there are several reports of negative side-effects due to using the drugs that are not confirmed by the ministry of health. Many of these drugs are handmade and trafficked into the country. They are rarely distributed by authorized pharmacies and mostly found in hair salons, gym clubs, and herbal medicine shops. Unfortunately, these drugs, mostly imported from China, are highly popular, while they mostly cause dangerous side effects (12).

These so-called herbal drugs are intensively advertised in satellite TV channels that are not controlled by legal

\*Correspondence to: Bahman Haj Mohammadi. MSC Student, Department of Toxicology & Pharmacology, Faculty of Pharmacy, Islamic Azad University (IAUPS), Tehran, Iran.

Email: bhph\_1388@yahoo.com

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authorities in Iran. It is not possible to tell by visual examination of the drugs and the packaging if the drugs contain psychedelic compounds (e.g., amphetamine, methamphetamine, and methyl dioxide methamphetamine) and other illicit drugs (12). The users need to know that if a drug is not approved by the ministry of health, it is either ineffective or contains illicit compounds that may cause side effects. Therefore, the first sign of an effective weight loss drug is a license issued by the ministry of health. The growing trend of using illicit weight loss drugs is witnessed in the European, North American, and Asian countries as well and several studies have been carried out to survey the illicit compounds used in these so-called herbal drugs. These studies have reported different and inconsistent results. The most common illicit compounds used in such drugs are sibutramine, fenfluramine, ephedra, and caffeine. All these compounds are illicit and create side effects like xerostomia, hand tremor, increased blood pressure, sleep disorders, loss of appetite, palpitation, liver and kidney damage, cardiovascular problems, and even death (13, 14).

Taking into account the growing rate of using weight loss pills and capsules and that youths are the main consumers, the present study is an attempt to determine the effective substance of prevalent super slim weight loss capsules.

**METHODS**

A pilot study was carried out at first to determine the sample group size. Based on the results of the pilot study and assuming that sibutramine was the effective substance, sample group size was obtained using the formula  $N = Z^2 \cdot P(1-P) / D^2$ . Through this, the sample size was obtained equal to 26 capsules. The samples were collected from five urban districts of Tehran city (north, south, west, east, and center) from pharmacies and herbal drug shops in 2012. Determining the sample size was based on the prevalence of drug use and drug poisoning.

The samples were coded based on color and packaging and the 26 samples were categorized into 11 groups (K, M, I, H, G, F, E, D, C, B, A), and these 11 groups were in turn categorized into subgroups based on colors. The subgroups are (A1, A2, A3, B, C1, C2, C3, D1, D2, D3, E1, E2, E3, F1, F2, G1, G2, H, I, M1, M2, M3, M4, M5, M6, K).

To prepare the samples, each capsule was weighed separately and 0.5gr of each one was mixed with 2.5ml methanol. The mixture was poured into a tube and the opening was sealed using paraffin. To ensure obtaining a perfect solution, the tubes were placed on a vortex device and then on an ultrasound device for 30min. The solution was then filtered by 0.45µl filters and brought up to volume using methanol (5ml). After preparation, the samples were injected into a high-performance liquid chromatography device (HPLC) at mobile phase containing water, methanol, and trimethylamine (0.5+79.5+20, v/v/v) with pH=50.65. After 30min, the peaks were recorded for further analysis. For internal standard, a material similar to sibutramine in terms of structure and RT less than that of sibutramine was used. To this end, zolpidem with RT of 3.2, which is less than the RT of sibutramine (RT=4.3), was selected.

Afterwards, 0.059gr of standard sibutramine was papered

and brought up to volume using 25ml of methanol. Afterwards, the prepared stock was used to prepare different concentrations (12.5µg/ml, 25µg/ml, 50µg/ml, 100µg/ml, 200µg/ml, and 500µg/ml.)

After obtaining a suitable internal standard – i.e., zolpidem – 0.025gr of zolpidem was weighed and solved in an HPLC grade water solution brought to 25ml volume and 1mg/ml density. 50µl of the solution was then added to the standard densities of sibutramine (5µg/ml, 10µg/ml, 12.5µg/ml, 25µg/ml, 50µg/ml, 100µg/ml, 200µg/ml, 500µg/ml, and 1000µg/ml).

The samples were injected into the HPLC starting with the one with the lowest concentration. It is notable that three vials of each concentration were prepared and each of them was injected separately into the device. The mean area under the curve was measured for each concentration and a standard diagram was drawn.

**RESULTS**

The findings showed that prevalent super slim weight loss capsule was not equally distributed in Tehran city; instead, it was easily accessible in the east, west and south of the city and hard to find in the north of the city.

The color of the packages clearly showed that the capsule was not produced by a pharmaceutical company as the products were categorized into 11 groups based on the color. Each capsule contained a powder with different color ranged from light to dark brown. The prepared samples with methanol had different colors including dark green, light green, light red, and orange. The weight of the capsules is listed in Table 1 and it is notable that they were not identical in terms of weight.

**Table 1. Weight of the super slim capsules**

No.	Sample name	Weight (gr) (n=6)
1	A1	0.3958±0.03
2	A2	0.3754±0.01
3	A3	0.2658±0.02
4	B	0.3562±0.03
5	C1	0.328±0.04
6	C2	0.3369±0.03
7	C3	0.3310±0.01
8	D1	0.2148±0.03
9	D2	0.2423±0.04
10	D3	0.3699±0.02
11	E1	0.3532±0.01
12	E2	0.3380±0.02
13	E3	0.3377±0.02
14	F1	0.2796±0.03
15	F2	0.2920±0.04
16	G1	0.3205±0.01
17	G2	0.2703±0.04
18	H	0.3118±0.02

Table 1. Continued

No.	Sample name	Weight (gr) (n=6)
19	I	0.3366±0.03
20	M1	0.3158±0.02
21	M2	0.3583±0.01
22	M3	0.3628±0.01
23	M4	0.3761±0.04
24	M5	0.3615±0.02
25	M6	0.3398±0.03
26	K	0.2838±0.01

The prepared standards of sibutramine at 12.5µg/ml, 25µg/ml, 50µg/ml, 100µg/ml, 200µg/ml, and 500µg/ml concentrations were injected into HPLC for three times and the mean area under the curve was calculated for each concentration. The linear equation obtained from this standard ( $x=665452$ ,  $y=42018$ ) was computed with correlation coefficient of 0.9901 ( $R^2=0.9901$ ) (Figure 1).

After preparing the standard zolpidem as the internal standard, 50 µl of which was added to each concentration of sibutramine (50 µg/ml, 10 µg/ml, 12.5 µg/ml, 25 µg/ml, 50 µg/ml, 100 µg/ml, 200 µg/ml, 500 µg/ml, and 1000 µg/ml). Each concentration was injected into HPLC for three times and mean area under the curve was measured after 15min. The area under the curve of zolpidem was then divided by that of sibutramine before drawing the standard curve (Table 2). Afterwards, the linear equation ( $y=0.052$ ,  $x+0.127$ ,  $R^2=0.999$ ) was obtained (Figure 2).

The limit of concentration, linear and zolpidem internal standard (50µg/ml), was added to each standard sample of sibutramine. The results of quantitative analysis of super

Table 2. Area under the curve for sibutramine and zolpidem in the standard samples

Area under the curve (zolpidem)	Area under the curve (sibutramine)	Concentration
1366351	441187	5 µg/ml
1139207	602312	10 µg/ml
1174834	1026831	12.5 µg/ml
1152774	1878888	25 µg/ml
1024190	3028800	50 µg/ml
1035068	5779151	100 µg/ml
1057278	10422673	200 µg/ml
9855671	34679128	500 µg/ml
955671	50941493	1000 µg/ml

slim capsule samples showed that the pharmaceutical concentration of sibutramine in the super slim capsules was between 33.51µg/ml and 286.78µg/ml (samples B1, D1, D2, E1, E2, E3, M4, M5, and M1). Out of 26 prevalent super slim weight loss capsules, nine (34.62%) contained sibutramine, seven (26.92) contained mirtazapine (A1, G1, C1, C2, C3, D3, K), and ten (38.46%) contained no effective pharmaceutical substance (M6, M3, M2, I, H, G2, F2, F1, A3, A2). The results of injecting prevalent super slim weight loss capsules and zolpidem into HPLC were then obtained Table 3). Afterwards, chromatograms of sibutramine calibration curves (Figure 3) and super slim capsule (Figure 4) were produced.

DISCUSSION

Obesity and overweight are global diseases. Obesity treatment is not aimed at lowering one’s weight to a normal level, but it rather tries to cut 10% of total body weight. Doing so decreases the risk of many diseases caused by obesity (15).

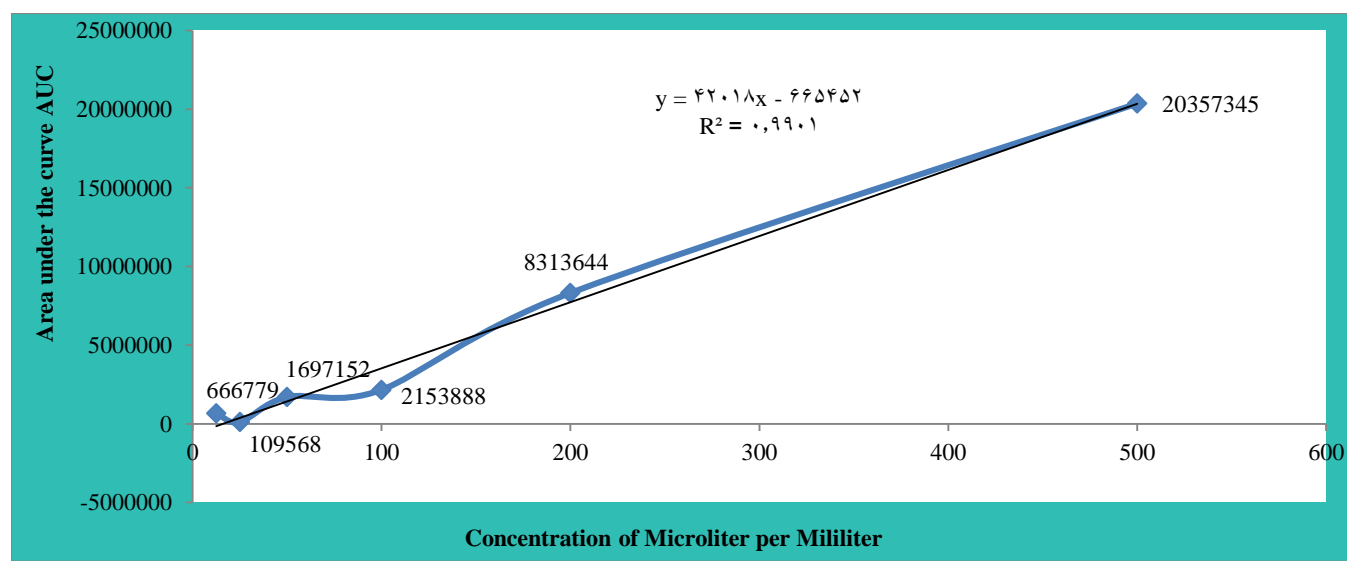


Figure 1. Linear equation of sibutramine standards

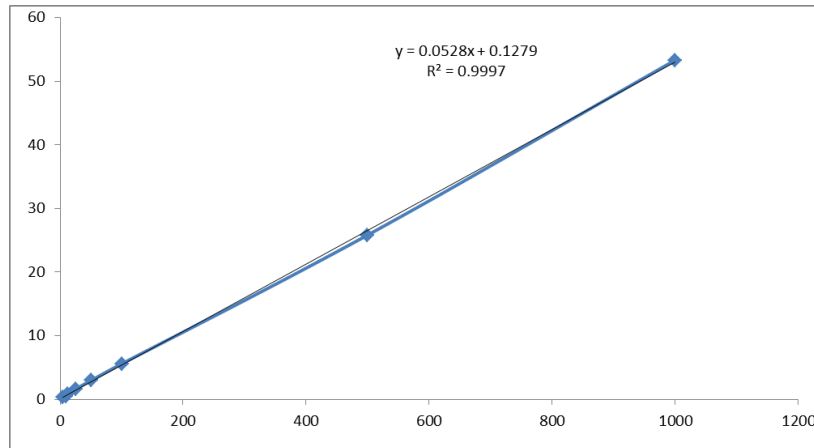


Figure 2. Calibration curve obtained from sibutramine standard

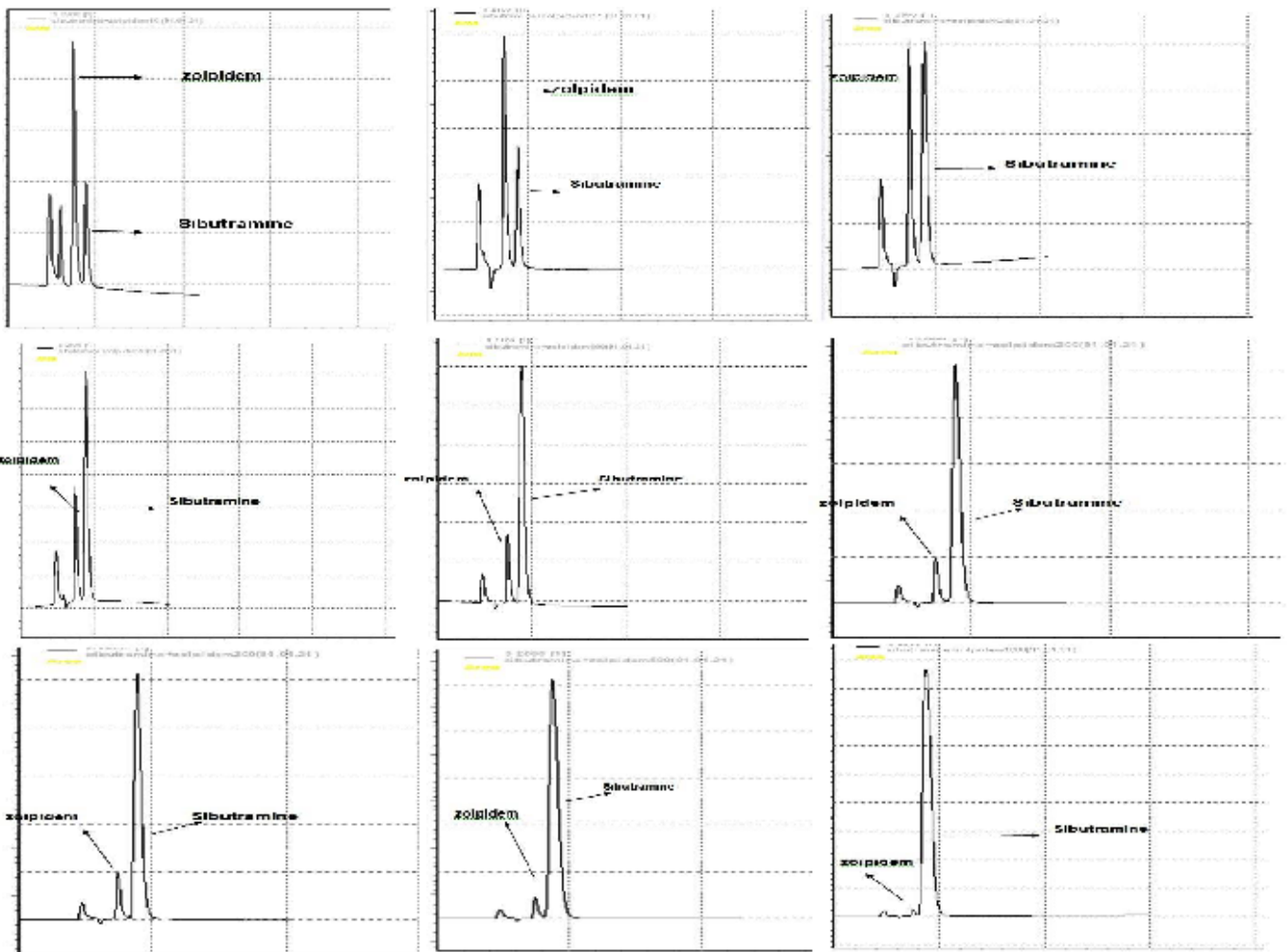


Figure 3. Chromatograms of sibutramine calibration curve



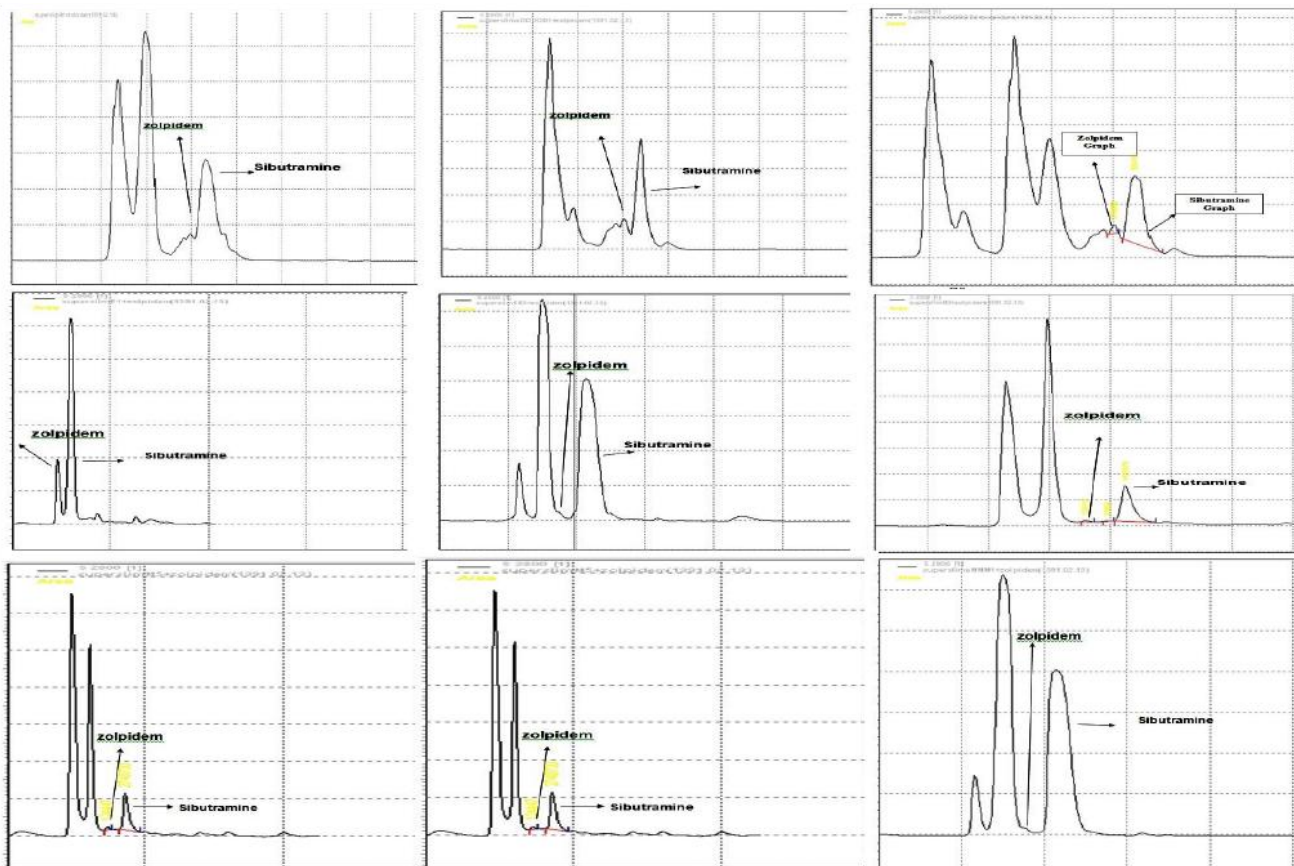


Figure 3. Chromatographs of super slim capsules calibration

Table 3. The results obtained by injecting prevalent super slim weight loss capsules and zolpidem into HPLC

Concentration of sibutramine	Area under the curve (zolpidem)	Area under the curve (sibutramine)	Sample No.
299.3 µg/ml	1084951	17029799	B1
105.8 µg/ml	1071560	5803043	D1
149.28 µg/ml	1120581	8841945	D2
41.59 µg/ml	1105671	2542925	E1
286.78 µg/ml	1176251	17701240	E2
80.44 µg/ml	1037531	4453676	E3
33.51 µg/ml	1136472	2129057	M4
44.86 µg/ml	1115681	2748730	M5
280.82 µg/ml	1192021	17564173	M1

Studies have shown that only 20% of individuals with overweight manage to lower their weight in long run – i.e., at least 10% weight loss in one year. The standards set by the USA Food and Drug Administration (FDA) for treatment of obesity include significant statistics of weight loss of at least 5% in one year or 5% weight loss in more than 35% of the patients (16).

According to the FDA, drug therapy for obesity must be based on metabolic biomarkers including blood pressure, lipids, and blood sugar. By finding the growing trend of

obesity in the industrial societies including Iran as an opportunity, suppliers may flood the market with diverse weight loss drugs. Among these drugs, are herbal based drugs that have become highly popular due to heavy advertisement and the public belief that herbal drugs are risk free. The mere claim that herbal ingredients are used in a product is no guarantee for safety of the product and there must be adequate documents and information about the ingredients and the side effects of using such produces (14). Following the extensive advertisements for prevalent super slim weight

loss drug as a completely herbal based drug, the FDA announced that this drug consists Sibutramine, Rimonabant, Phenytoin, and Bumetanide (17).

Surveys of the effective substances in prevalent super slim weight loss capsule were done using HPLC with mobile phase of water, methanol, and trimethylamine and zolpidem as an internal standard. Based on the findings, standard diagrams were developed for different concentrations of sibutramine and each super slim capsule sample.

Sibutramine, an illicit substance, is mostly used as one of the main ingredients in weight loss capsules imported to Iran (18). The most common side effect of this compound is higher risk of cardiovascular conditions, heart failure, and sudden death. In light of such side effects, this substance has been declared illegal in the West. There are studies that argue sibutramine is coincident with psychological and mood changes. However, it is used as a medicine in some countries at 5-15mg/day dosage (11).

In a study entitled "Identification and determination of synthetic pharmaceuticals as adulterants in eight common herbal weight loss supplements," Khazan examined six brands of so-called herbal medicines through gas chromatography-mass spectrometry. He measured the quantity of sibutramine, phenytoin, and phenolphthalein in the samples. The results confirmed that the samples contained sibutramine and the brands Original Super Slime and Fast Slim had the highest levels of sibutramine. In addition, the capsules contained other illicit compounds that were not listed in the ingredient list (19).

In a study titled "Over-the-counter Weight-Loss Herbal Supplements in Egypt: Label Claim, Microbiological, Pharmaceutical Quality and Safety Assessments," Ahmed examined weight loss products in terms of safety and efficiency between 2015 and 2017. Six products were examined through HPLC method including Zotreem Plus®, Zotreem Extra®, Malaysian Super Slim®, AB Slim®, Chinese Super Slim® and Metabolites®. The results showed that the products contained sibutramine, sildenafil, phenolphthalein, orlistat, and narcotics to some extent. The consumers of these products reported side effects like depression, diarrhea, and high blood pressure (20).

## CONCLUSION

The results showed not only the super slim capsules available in Iran market are not herbal based, they even contain sibutramine and mirtazapine synthetic substances. Pharmaceutical concentration of sibutramine in the capsules ranged from 33.51µg/ml to 286.78µg/ml. In addition, only 34.62% of the samples contained sibutramine, 26.92% contained mirtazapine, and 38.46% contained no pharmaceutical substance (placebo). It is not easy to generalize the findings to other countries and more studies are required in this regard.

The study showed that super slim capsules are supplied by different producers so that the color, packaging, color of the materials inside capsules, ingredients and pharmaceutical category of the samples were not the same.

Other studies have reported that herbal weight loss capsules in the market contain different pharmaceutical

substances including Medaphynine, ephedrine, metformin, theophylline, caffeine, Diethylpropion, Orlistat, Rimonabant, and phenytoin. The present study, however, also found mirtazapine along with sibutramine in the samples. There is no report of finding mirtazapine in herbal weight loss capsules by other studies (21).

Analogous to Mianserin that induces secretion of noradrenaline, Mirtazapine is a Piperazine Azepine that induces secretion of serotonin indirectly and through adrenergic synapsis receptor block ( $\alpha_2$ ). Mirtazapine is also an antagonist of H1 histamine receptor, induces relaxation effects, and acts as a trivial antimuscarinic activator (21).

Given the easy access to weight loss drugs in Iran market and the untrue advertisements about herbal base and natural formulation of such drugs, the consumers of such products are at high health risks. The data obtained through analyzing prevalent super slim weight loss drug showed that not only they are not herbal based but also contain synthetic substances known as sibutramine and mirtazapine. The ministry of health is recommended to inform and warn the public about these drugs and test their effectiveness and safety. The entity is required to declare its recommendations to the market based on the pertinent marketing regulations.

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## REFERENCES

1. Fryar CD, Carroll MD, Ogden CL. Prevalence of overweight, obesity, and severe obesity among children and adolescents aged 2–19 years: United States, 1963–1965 through 2015–2016. United States: National Center for health statistics; 2018.
2. World Health Organization. World Health Organization Fact Sheet N311: Obesity and Overweight. Geneva, Switzerland: World Health Organization;2018.
3. World Health Organization. Obesity and overweight. Fact sheet N 311. Available from <http://www.who.int/mediacentre/factsheets/fs311/en/>. 2012.
4. Fallahzadeh H, Saadati H, Keyghobadi N. Estimating the Prevalence and Trends of Obesity in Iran Populations from 2000 to 2011: A Meta-Analysis Study. *J Shahid Beheshti Uni Med Sci* 2017;25:681-9.
5. Mirzazadeh A, Salimzadeh H, Arabi M, Navadeh S, Hajarizadeh B, Haghdoost AA. Trends of Obesity in Iranian Adults from 1990s to late 2000s; a Systematic Review and Meta-analysis. *Middle East J Dig Dis* 2013; 5(3):151.
6. Dietz WH, Baur LA, Hall K, Puhl RM, Taveras EM, Uauy R, Kopelman P. Management of obesity: improvement of health-care training and systems for prevention and care. *The Lancet* 2015; 385:2521-33.
7. Corazza O, Simonato P, Corkery J, Trincas G, Schifano F. "Legal highs": safe and legal "heavens"? A study on the diffusion, knowledge and risk awareness of novel psychoactive drugs among students in the UK. *Riv Psichiatr* 2014;49:89-94.

8. Kelishadi R, Haghdoost AA, Sadeghirad B, Khajehkazemi R. Trend in the prevalence of obesity and overweight among Iranian children and adolescents: a systematic review and meta-analysis. *Nutrition* 2014;30:393-400.
9. Basher A, Khokon K, Kuch U, Toennes S.W, Faiz A. Unknown Herbal Poisoning with Fatal Outcome. *Asia Pac J Med Toxicol* 2018; 7:112-4.
10. Yousefi M, Afshari R. Measurement of Methanol Contents in Most Commonly Used Herbal Distillates in Mashhad. *Asia Pac J Med Toxicol* 2014; 3:5.
11. Khazan M, Hedayati M, Kobarfard F, Askari S, Azizi F. Identification and determination of synthetic pharmaceuticals as adulterants in eight common herbal weight loss supplements. *Iran Red Crescent Med J* 2014;16:e15344.
12. Yun J, Choi J, Jo CH, Kwon K. Detection of Synthetic Anti-Obesity Drugs, Designer Analogues and Weight-Loss Ingredients as Adulterants in Slimming Foods from 2015 to 2017. *J Chromatogr Sep Tech* 2018;9:2.
13. Onakpoya IJ, Heneghan CJ, Aronson JK. Post-marketing withdrawal of anti-obesity medicinal products because of adverse drug reactions: a systematic review. *BMC Med* 2016;14:191.
14. Vosough M, Baheri T, Shekari N, Salemi A. Detection of Illicit Drugs in Herbal Weight Loss Products in Iran. *Tabriz Uni Med Sci Health Serv* 2014;36:86.
15. Bersani FS, Coviello M, Imperatori C, Francesconi M, Hough CM, Valeriani G, et al. Adverse psychiatric effects associated with herbal weight-loss products. *Biomed Res Int* 2015;2015:120679.
16. Kothadia JP, Kaminski M, Samant H, Olivera-Martinez M. Hepatotoxicity Associated with Use of the Weight Loss Supplement *Garcinia cambogia*: A Case Report and Review of the Literature. *Case Reports Hepatol* 2018 Mar 12;2018:6483605.
17. Seeff LB, Bonkovsky HL, Navarro VJ, Wang G. Herbal products and the liver: a review of adverse effects and mechanisms. *Gastroenterology* 2015;148:517-532.e3.
18. Gilard V, Balayssac S, Tinaugus A, Martins N, Martino R, Malet-Martino M. Detection, identification and quantification by 1H NMR of adulterants in 150 herbal dietary supplements marketed for improving sexual performance. *J Pharm Biomed Anal* 2015;102:476-93.
19. Khazan M, Hedayati M, Kobarfard F, Askari S, Azizi F. Identification and determination of synthetic pharmaceuticals as adulterants in eight common herbal weight loss supplements. *Iran Red Crescent Med J* 2014;16:e15344.
20. Ahmed N, Nounou MI, Abouelfetouh A, El-Kamel A. Over-the-counter Weight-Loss Herbal Supplements in Egypt: Label Claim, Microbiological, Pharmaceutical Quality and Safety Assessments. *Med Princ Pract* 2018 [Epub ahead of print]
21. Deconinck E, Verlinde K, Courselle P, De Beer JO. A validated Ultra High Pressure Liquid Chromatographic method for the characterisation of confiscated illegal slimming products containing anorexics. *J Pharm Biomed Anal* 2012;59:38-43.