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DETECTION AND QUANTIFICATION OF CYPROHEPTADINE AND DEXAMETHASONE AS ADULTERANTS IN HERBAL MEDICINES AND DIETARY SUPPLEMENTS MARKETED FOR WEIGHT GAIN

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Herbal medicines and dietary supplements have become more well-liked throughout the world as viable alternatives to pharmaceutical medicines. The aim of this study is to detect and quantify any adulteration with cyproheptadine and dexamethasone in herbal medicines and dietary supplements claimed to be natural and used for weight gain in the Iraqi market. Qualitative and quantitative spectrophotometric analysis of selected herbal medicines and dietary supplements used for weight gain sold in community pharmacies in Mosul City, Iraq. The samples were screened for cyproheptadine and dexamethasone using a UV-spectrophotometer. Cyproheptadine was detected in eight out of ten formulations at a dose range from (2.86 to 10.46) mg/dosage unit. Dexamethasone was detected in all formulations at doses ranging from (1.39 to 36.42) mg/dosage unit. The method was validated for accuracy, precision, the limit of detection, the limit of quantitation, specificity, and linearity. The majority of marketed herbal medicines and dietary supplements, that were claimed to be natural, were adulterated with large quantities of pharmaceutical ingredients that can cause potentially serious adverse effects. The increasing trend in the utilization of herbal medicines and dietary supplements together with increased levels of adulteration calls for the development of easy simple and fast detection methods and informs health authorities and healthcare professionals about adulterated products and their contents.

Keywords: *Detection; Adulteration; Cyproheptadine; Dexamethasone; Spectrophotometry*

INTRODUCTION

In recent years, herbal medicines and dietary supplements have become more well-liked throughout the world as viable alternatives to pharmaceutical medicines[1]. Due to the widespread perceptions among people around the world, that herbal medicines are natural and therefore they are safer than conventional pharmaceutical medicines and can be used without medical supervision, they are extremely popular[2]. Furthermore, herbal medicines and dietary supplements users trust the labels placed on these products including the ingredients and indications[3]. Because the majority of these herbal medicines and dietary supplements are subjected to food legislation policies and are sold as over-the-counter nutritional supplements, they are not required to undergo clinical trials to ensure their efficacy and safety, or quality control[4].

According to the United States Pharmacopeia, adulteration can be defined as perpetrated and planned change in the ingredients of herbal, dietary, or pharmaceutical products for economic reasons and to gain more profits[5]. This can be made via complete or partial substitution of the ingredients of a product with non-approved, less effective, or less costly ingredients[6]. Studies have investigated the adulteration of herbal medicines and dietary supplements with undisclosed pharmaceuticals, often exceeding the maximum prescribed dosage. Unfortunately, customers are unaware that these products are counterfeit or adulterated[7].

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The industry of herbal medicines and dietary supplements is growing sharply with annual sales exceeding 152 billion dollars in 2021 and expected to flourish and achieve 300 billion dollars by 2028[8]. According to estimates from the World Health Organization (WHO), at least 80% of people in developing nations still only receive primary health care from traditional medicine, which consists mainly of herbal medicines[9]. Undetected medicines and synthetic substances found in herbal medicines and dietary supplements can be hazardous and frequently combined with other pharmaceutical prescription medicines, leading to unfavorable outcomes that may even be fatal[6]. As such, it is not always simple for customers to distinguish between genuine and adulterated products[1].

However, the extensive use of herbal medicines and dietary supplements made them a lucrative target for fraudulent manufacturers to produce low-quality or adulterated products by using alternative herbs and/or adding synthetic pharmaceuticals or chemicals without disclosing these substances[10]. Studies showed that weight loss, weight gain, and aphrodisiac agents were the most commonly adulterated products sold in community pharmacies, herb shops, and online. The review of the literature showed that the majority of studies were conducted to analyze and detect adulterants in weight loss and aphrodisiac agents[11-14]. However, there is a paucity of research to analyze and detect adulterants in weight gain products. Cyproheptadine and dexamethasone were the most frequently reported adulterants found or expected to be found in herbal medicines used for weight gain[15,16]. In 2018, an Iranian study analyzed sixty herbal medicines claimed to be natural and to be used for weight gain in Iran. About half of the analyzed products were found to be adulterated with cyproheptadine and dexamethasone[16].

Cyproheptadine is an antihistamine with appetite-stimulant effects, acting as a serotonin receptor antagonist at the appetite center of the hypothalamus **(Fig. 1A)**[17]. It was first used to treat allergic reactions; however, its main use nowadays is to increase appetite in malnourished and/or underweight patients with a number of medical conditions[18]. Dexamethasone is a potent synthetic glucocorticoid with anti-inflammatory and immunosuppressive properties; therefore, it is used in the treatment of inflammatory and autoimmune diseases **(Fig. 1B)**[19]. Dexamethasone is added to weight gain products due to its action in appetite stimulation and increased visceral and truncal fat deposition that leads to weight gain[20]. Despite its wide range of uses, dexamethasone like other glucocorticoids is associated with a multiplicity of side effects depending on dose, duration, frequency, time of day, and mode of administration[21].

Due to the wide availability of herbal medicines and dietary supplements in Iraqi markets the lack of regulations and less stringent supply chains, it is expected that herbal medicines and dietary supplements adulteration is common in such an environment. The extent and nature of adulteration of herbal medicines and dietary supplements that are used in weight gain are unknown in Iraq[22]. The current study aims to detect and quantify cyproheptadine and dexamethasone in herbal medicines and dietary supplements used for weight gain available in Iraqi pharmacies using a validated, easy, and fast method.

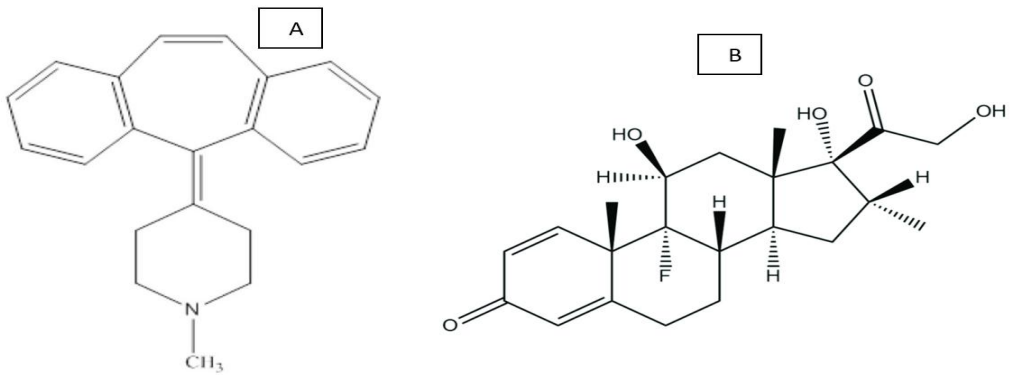

Fig. 1: Chemical structures of A) cyproheptadine and B) dexamethasone[23,24]

EXPERIMENTAL

Standards and reagents

Cyproheptadine HCl and dexamethasone were used as reference substances. They were obtained as gifts from Pioneer Company for pharmaceutical industries and the State Company for Drug Industry and Medical Appliances (SDI) in Iraq, respectively. Cyproheptadine tablets containing 4 mg manufactured by Micro Labs Limited, (India), and dexamethasone tablets containing 8 mg manufactured by Koçak Limited, (Turkey), were bought from local pharmacies. Analytical grade methanol and freshly prepared distilled water were mixed in a 1:4 ratio to prepare a cosolvent for cyproheptadine sample preparation[25] and a 1:2 ratio to prepare a cosolvent for dexamethasone[26].

Collection and identification of tested samples

Ten herbal medicines and dietary supplements, that claimed to be natural and used for weight gain, were bought from local pharmacies, herb shops, herb apothecaries, and online stores. **Table 1** summarizes the specifications of the purchased and analyzed products.

Equipment

GENESYS™ 180 UV-visible spectrophotometer with wavelength precision of 2 nm, and matched quartz cells with a 1 cm optical path length was used to measure the absorbance of cyproheptadine and dexamethasone in the freshly prepared cosolvent of (water and methanol) for each drug. Methanol: water solution was used as a blank.

Standards and sample solutions preparation

Preparation of standard stock solution of cyproheptadine and dexamethasone

To prepare a stock standard solution of cyproheptadine and dexamethasone, 25 mg of each reference drug was weighed individually and dissolved in the specified freshly prepared cosolvent in a 50 mL volumetric flask. The resultant final concentration for each drug is 0.5 mg/mL.

Preparation of sample solutions for herbal medicines and dietary supplements

From each product, ten tablets were taken from the package. Using a three-digit weighing scale, the weight of these tablets was recorded and their average weight was calculated separately. Then, the tablets of each product were pulverized to a fine powder by a mortar and a pistol. From the pulverized powder of each product, an equivalent of 10 mg of cyproheptadine HCl and 10 mg of dexamethasone were separately transferred into a 100 ml volumetric flask and dissolved in 100 ml of specified cosolvents for cyproheptadine and dexamethasone. Then each flask was shaken using an ultrasonicator for 15 minutes. This is followed by filtration of the solution using Whatman filter paper no. 41. Subsamples of these solutions were diluted with distilled water to obtain final concentrations of 100 μg/ml[16].

Table 1 : Specifications of the analyzed products.

Samples	Ingredients	Origin/ producing company	Dosage form	Collection place	Collection date	Production date	Expiration date
S1 FY	Noretnanderione, vitamins A, C, D, E, calcium, magnesium, testosterone decanoate, human growth hormone, and zinc	USA/ CYT Genix labs	Tablets	Iraq, Mosul, Community Pharmacy	11/2023	03/2020	03/2024
S2 FP	Noretnanderione, vitamins A, C, D, E, calcium, magnesium, testosterone decanoate, human growth hormone, and zinc	USA/ CYT Genix labs	Tablets	Iraq, Mosul, Community Pharmacy	11/2023	03/2020	03/2024

Table 1: Continued.

S3 GG	Radix angelicae sinensis, Rhizoma ligustici chuanxiong, Cordyceps sinensis, Radix polygoni multiflora, Cortex cinnamomi cassia, Radix morindae officinalis, Cornu cervi pantotrichum, Cortex eucommiae ulmoides, Radix panax ginseng, Rhizoma gastrodiae elata, Rhizoma atractylodis macrophalae, Rhizoma anemarrhenae asphodelides, Radix polygalae tenuifolia, Radix astragali seu hedysari, Rhizoma dioscoreae opposite, Radix rehmanniae glutinosa, Fructus lycii barbarum, Poria cocos, Radix codonopsis pilosulae, Semen ziziphi spinosae, Radix glycyrrhizae uralensis	China/ Kianpi	Capsules	Iraq, Mosul, Herb shop	10/2023	2/2023	2/2025
S4 HF	Magnesium, zinc, dehydroepiandrosterone, copper, ginkgo biloba, vitamins B_1, B_2, B_{12}, and C	USA/ DSL labs	Tablets	Online	10/2023	4/2022	4/2025
S5 HS	Magnesium, zinc, dehydroepiandrosterone, copper, ginkgo biloba, vitamins B_1, B_2, B_{12}, C and D	USA/ DSL labs	Tablets	Online	10/2023	4/2022	4/2025
S6 JG	Ginger, vitamins B2, B3, inositol, dried Mugwort liquid extract	USA/ JP Limited	Tablets	Iraq, Mosul, Community Pharmacy	12/2023	1/2022	1/2025
S7 JF+	Magnesium, zinc, copper, ginkgo biloba, malt powder, vitamins B_1, B_2, B_{12}, C, and dandelion	USA/ JP Limited	Tablets	Iraq, Mosul, Community Pharmacy	11/2023	2/2023	2/2026
S8 JS+	Magnesium, zinc, copper, ginkgo biloba, malt powder, breweries yeast, and Foeniculum vulgare	USA/ JP Limited	Tablets	Iraq, Mosul, Community Pharmacy	11/2023	2/2023	2/2026
S9 PA	Vitamins B_1, B_2, B_3, and lutein	Germany / unknown	Tablets	Iraq/ Baghdad/ Herb apothecary	12/2023	6/2013	1/2025
S10 W+	Ginger, licorice, thyme, Majorana, and eucalyptus leaves	Iraq/ Alattar Land	Capsules	Iraq/ Baghdad/ Herb apothecary	12/2023	9/2023	9/2024

Calibration curve

Standard stock solutions for cyproheptadine and dexamethasone were suitably diluted with specified cosolvent to obtain concentrations ranging from 0.3-20 µg/ml. The absorbance of these solutions was measured using a UV spectrophotometer. A wavelength of 286 nm was selected for cyproheptadine and 241 nm for dexamethasone for measuring the absorbance of these agents in the standard solutions as well as in sample solutions. From the measured absorbance against each concentration, a calibration curve was plotted (**Fig.** 2).

Method of validation of the parameters

The proposed method was validated according to the International Council for Harmonization (ICH) guidelines[27].

Specificity

To determine the specificity of the method utilized, by measuring the absorbance of the blank, placebo, analyte solutions that contain standard cyproheptadine and dexamethasone. The system response was analyzed to determine if there were any overlaps or interference with the reactions to cyproheptadine and dexamethasone at 286 and 241 nm respectively[28,29].

Accuracy

Despite the fact that the used methods were validated by Friedrich et al., (2009) and Patil et al., (2019) studies for dexamethasone and cyproheptadine, respectively[26,28], the accuracy of the used methods were further checked by determining % of recovery. This was performed by measuring the absorbances and concentrations of a known amount of cyproheptadine and dexamethasone tablets at three different times. The absorbance, concentration, % of recovery, standard deviation (SD), and relative standard deviation (RSD) were recorded. The following formula was used to determine the % recovery (30):

$$\% \text{ of Recovery} = Cm / Ck \times 100$$

where Cm represents the concentration measured of the drug estimated, and Ck represents the known concentration of the drug.

Linearity

The linearity of the suggested UV spectrophotometric methods was assessed through the examination of different concentrations of standard solutions of cyproheptadine and dexamethasone. Beer's law was obeyed for the methods. Graphs were plotted for concentration versus absorbance. The linearity of cyproheptadine was obtained using six concentrations (0.312, 0.625, 1.25, 2.5, 5, and 7.5 20 µg/mL) of cyproheptadine and (1, 2, 3, 4, 5, and 6 µg/mL) of dexamethasone. Good linear relationships (R^2=0.9946) for cyproheptadine and (R^2=0.9735) for dexamethasone were observed between the concentrations and the corresponding area under the curve. The regression analysis was conducted for slope, intercept, and correlation coefficient values. The equation of the calibration curve obtained were (y=0.4601x+0.047) and (y=0.4527x+0.2254) for cyproheptadine and dexamethasone, respectively.

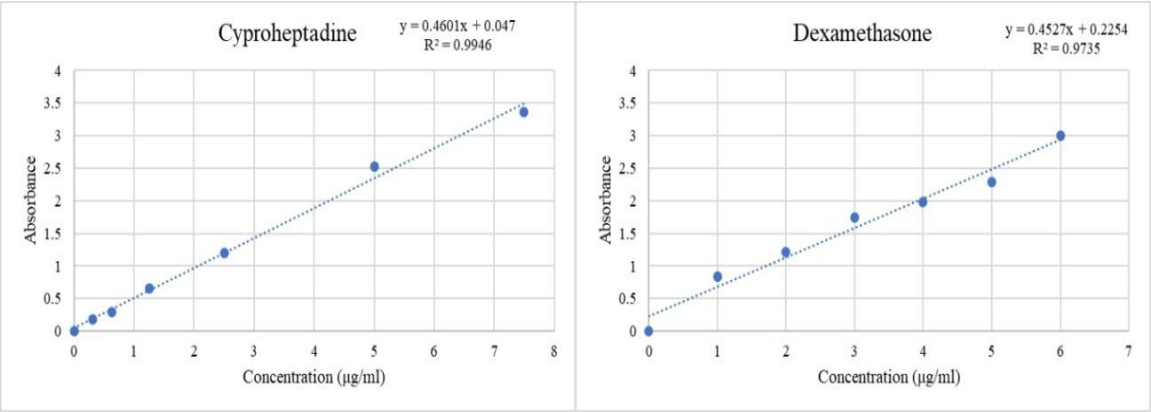

Fig. 2: Calibration curves for cyproheptadine and dexamethasone.

Limit of detection (LOD) and limit of quantification (LOQ)

The limit of detection (LOD) and limit of quantification (LOQ) of the cyproheptadine and dexamethasone were separately determined based on methods of the intercept and the average value of the slope. (i.e., 3.3 for LOD and 10 for LOQ) ratio using the following equations designated by ICH guidelines (27). LOD = 3.3 σ/S, LOQ = 10 σ /S. Where, σ = the standard deviation of the response, S = slope of the calibration curve.

RESULTS AND DISCUSSION

Results

Despite the fact that the aims of this study were to detect and quantify the presence of cyproheptadine and dexamethasone in herbal medicines and dietary supplements used for weight gain, it is also necessary to validate the used method. An easy, rapid, and eco-friendly spectrophotometric method to assay cyproheptadine and dexamethasone in tablets is required before using more sophisticated methods of detection like high-performance liquid chromatography. This method utilized a cosolvent (a mixture of methanol and water) and distilled water as blank.

The analysis starts with scanning for absorbance in a wavelength range between 190 and 600nm. However, the maximum absorption of cyproheptadine and dexamethasone were at 286 and 241nm respectively **(Fig. 3)**. A linear relationship was found between the absorbance at 286 and 241 nm and the concentration of cyproheptadine and dexamethasone, respectively. The results of the method validation for specificity, accuracy, linearity, LOD, and LOQ are shown in **Table 2**.

The reason for nuance differences found in our results and the results of Friedrich et al., (2009) and Patil et al., (2019) studies was attributed to the different techniques used in sample preparations, solvents used, and analysis parameters to determine LOD and LOQ (26, 28). Furthermore, it could be due to different samples and differences in batches analyzed.

The selected herbal medicines and dietary supplements were analyzed by measuring the UV absorption spectra at 286 and 241 nm to determine the presence of cyproheptadine or dexamethasone, respectively. The results showed spectrums corresponding to dexamethasone in all analyzed samples. However, cyproheptadine spectrum was detected in all of the samples except S1 and S2. Beer's law was obeyed for calculations.

In accordance with the absorbance results, cyproheptadine was detected in eight out of ten products at a dose range from (2.86 to10.46) mg/dosage unit while dexamethasone was detected in all formulations at doses ranging from (1.39 to 36.42) mg/dosage unit, as shown in **Table 3**. The labels attached to these products recommended two tablets daily for 4-6 weeks cycles. There were some statements on the labels such as: (super fat, fat face, starting fat).

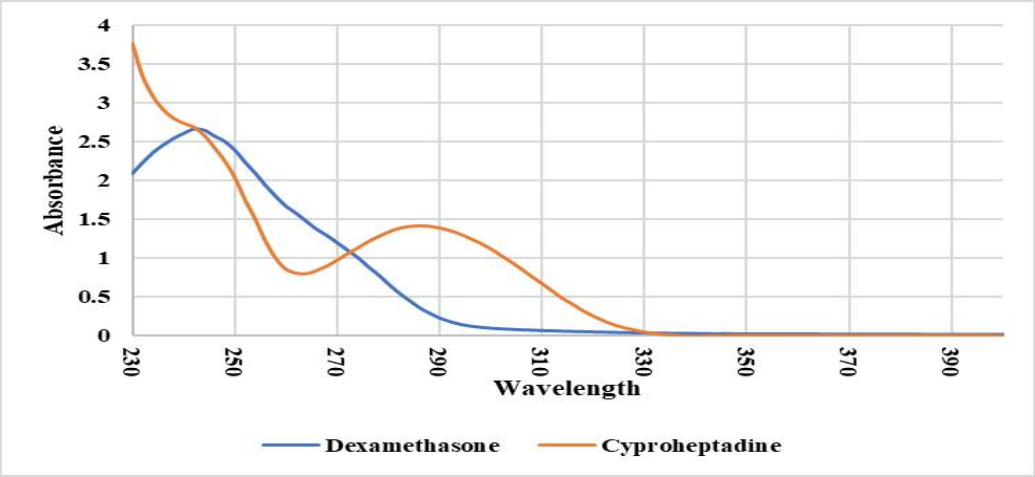

Fig. 3 : UV spectra of cyproheptadine and dexamethasone.

Table 2 : Summary of validation parameters.

Parameter	Cyproheptadine	Dexamethasone
λ-max	286	241
Linearity	0.9972	0.9866
Slope	0.38279	0.452679
Intercept	0.16751	0.225393
Accuracy % Recovery RSD	 % 96.1 2.27	 % 96.22 1.73
LOD	1.57	0.99
LOQ	5.23	3.01
Correlation coefficient	0.9946	0.9735

Table 3: Qualitative and quantitative results of the analyzed products.

Sample	Amount of cyproheptadine per dosage unit	Amount of dexamethasone per dosage unit
S1 FY	0	10.25
S2 FP	0	1.39
S3 GG	2.86	20.88
S4 HF	16.46	10.13
S5 HS	3.69	20.96
S6 JG	6.34	32.70
S7 JF+	3.21	14.07
S8 JS+	3.20	19.06
S9 PA	5.94	36.42
S10 W+	10.46	28.63

The results of this study were in line with an Iranian study conducted by Saberi et al, (2018), in which the analyzed herbal medicines that are used for weight gain were shown to be adulterated and the majority of the analyzed products contained cyproheptadine, dexamethasone, caffeine, and paracetamol[16]. Similarly, Friedrich et al, (2009) study investigated herbal medicines and found them to be adulterated with dexamethasone[26].

Furthermore, the results of this study also showed that the amount of cyproheptadine in some analyzed products (S10 W+ and S4 HF) was 2-4 times the recommended pharmacological dose for appetite stimulation per dosage unit. Furthermore, the labeled recommended dose for these products was two tablets per day. These high doses are potentially associated with the development of anticholinergic syndrome which includes agitation, confusion, restlessness, and delirium[31]. Similarly, the amount of dexamethasone found in the analyzed products (S3 GG, S5 HS, S6 JG, S9 PA, and S10 W+) was very high exceeding 20mg per dosage unit. Despite the fact that no clear cut-off dose for dexamethasone dose when used for appetite stimulation. However, studies found that doses of 2-8 mg of dexamethasone are effective in improving appetite stimulation in cancer patients[32,33]. Furthermore, hospital formularies in the United Kingdom recommend 2 – 4 mg daily of dexamethasone to improve appetite, fatigue, and well-being in palliative care[34]. High doses of dexamethasone that found adulterated products are potentially associated with hyperglycemia, high blood pressure, and Cushing syndrome. In addition to the direct adverse effects that adulterated herbal medicines and dietary supplements can cause, they can pose further health threats since they can precipitate drug-drug interactions and

aggravate toxicity from overdoses or concomitant administration with prescription medications taken simultaneously[35]. Therefore, the World Health Organization (WHO) doesn't classify adulterated herbal products as herbal medicine[36]. Additionally, dietary supplements are regarded as food by the European Medicine Agency and therefore they are subjected to the disposition of the General Food Law which sets standards for maintaining food safety. However, this is not applied in many other countries and is being abused by fraudulent manufacturers to produce adulterated herbal medicines and dietary supplements that can be sold in the market and/or advertised on the internet that promise weight gain quickly[37]. These products have a doubtful safety profile and may have negative effects that could be rather severe. Guidelines, including Good Manufacturing Practices for dietary supplements, pharmacovigilance systems, and accurate labeling of herbal medicines, were established by the WHO to provide useful information for monitoring the safety of herbal medicines and dietary supplements[38].

Conclusion

The present study showed that this simple and fast method reported was adequately applied for the identification and quantification of herbal medicine and dietary supplements marketed for weight gain that adulterated with cyproheptadine or dexamethasone. The process is also simple, and affordable, with high accuracy and precision. It could therefore be used in quality control laboratories where efficiency and affordability are essential concerns. Furthermore, the majority of marketed herbal medicines and dietary supplements, that were claimed to be natural, were adulterated with large quantities of pharmaceutical ingredients that can cause potentially serious adverse effects. The increasing trend in the utilization of herbal medicines and dietary supplements together with increased levels of adulteration calls for the development of easy simple and fast detection methods and informs health authorities and healthcare professionals about adulterated products and their contents.

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نشرة العلوم الصيدلية
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كشف وتقدير كمية السيبروهبتادين والديكساميثازون كمغشات في الأدوية العشبية المسوقة لزيادة الوزن الخلاصة

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أصبحت الأدوية العشبية والمكملات الغذائية أكثر شعبية في جميع أنحاء العالم كبدائل قابلة للتطبيق للأدوية الصيدلانية. الأهداف: كشف وقياس أي غش بالسيبروهيبتادين والديكساميثازون في الأدوية العشبية التي يُزعم أنها طبيعية وتستخدم لزيادة الوزن في السوق العراقية. التحليل الطيفي النوعي والكمي لأدوية عشبية مختارة تستخدم لزيادة الوزن والتي تباع في صيدليات المجتمع في مدينة الموصل، العراق. تم فحص العينات بحثًا عن السيبروهيبتادين والديكساميثازون باستخدام مقياس الطيف الضوئي للأشعة فوق البنفسجية. تم اكتشاف السيبروهيبتادين في ثمانية من أصل عشرة تركيبات بجرعة تتراوح من (٢.٨٦ إلى ١٠.٤٦) ملغم/وحدة جرعة. تم الكشف عن الديكساميثازون في جميع التركيبات بجرعات تتراوح بين (١.٣٩ إلى ٣٦.٤٢) ملغم/وحدة جرعة. تم التحقق من صحة الطريقة من حيث الدقة والدقة والحد من الكشف والحد من الكميات والنوعية والخطية. غالبية الأدوية العشبية المسوقة، والتي يُزعم أنها طبيعية، كانت مغشوشة بكميات كبيرة من المكونات الصيدلانية التي يمكن أن تسبب آثارًا جانبية خطيرة محتملة. إن الاتجاه المتزايد في استخدام الأدوية العشبية مع زيادة مستوى الغش يستدعي تطوير طرق كشف سهلة وبسيطة وسريعة وإبلاغ السلطات الصحية ومتخصصي الرعاية الصحية عن المنتجات المغشوشة ومحتوياتها.