



# Counterfeit formulations: analytical perspective on anorectics

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## Abstract

**Purpose** This paper examines the scope of anorectics in counterfeit weight-reducing formulations and provides insight into the present state of research in determining such adulterants. Analytical techniques utilised in profiling adulterants found in slimming products, including limitations and mitigation steps of these conventional methods are also discussed. The current legal status of the anorectics and analogues routinely encountered in non-prescription slimming formulations is also explored.

**Methods** All reviewed literature was extracted from Scopus, Web of Science, PubMed, and Google Scholar databases using relevant search terms, such as, ‘counterfeit drugs’, ‘weight loss drugs’, ‘weight-reducing drugs’, ‘slimming drugs’, ‘anorectic agents’, and ‘counterfeit anorexics’. Legislation related to anorectics was obtained from the portals of various government and international agencies.

**Results** Anorectics frequently profiled in counterfeit slimming formulations are mostly amphetamine derivatives or its analogues. Five routinely reported pharmacological classes of adulterants, namely anxiolytics, diuretics, antidepressants, laxatives, and stimulants, are mainly utilised as coadjuvants in fake weight-reducing formulations to increase bioavailability or to minimise anticipated side effects. Liquid and gas chromatography coupled with mass spectrometric detectors are predominantly used techniques for anorectic analysis due to the possibility of obtaining detailed information of adulterants. However, interference from the complex sample matrices of these fake products limits the accuracy of these methods and requires robust sample preparation methods for enhanced sensitivity and selectivity. The most common anorectics found in counterfeit slimming medicines are either completely banned or available by prescription only, in many countries.

**Conclusions** Slimming formulations doped with anorectic cocktails to boost their weight-reducing efficacy are not uncommon. Liquid chromatography combined with mass spectrometry remains the gold standard for counterfeit drug analysis, and requires improved preconcentration methods for rapid and quantitative identification of specific chemical constituents. Extensive method development and validation, targeted at refining existing techniques while developing new ones, is expected to improve the analytical profiling of counterfeit anorectics significantly.

**Keywords** Anorectics · Counterfeit weight loss formulations · Adulterants in slimming products · Amphetamine derivatives · Antihyperglycemic agents · LC–MS/MS

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## Introduction

Counterfeit pharmaceutical products represent an enormous global burden, and their sales have seen a tremendous surge in recent years, with its attendant threat to human health and

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public safety [1, 2]. An estimated 10% of the global pharmaceutical market consists of fake and substandard drugs [3]. Many countries in sub-Saharan Africa, Southeast Asia and Latin America, serve as fertile grounds, where about 30 to 60% of sold medicines are fraudulent [4]. The Pharmaceutical Security Institute (PSI) based on a seventeen consecutive year data on counterfeiting, recognized a permanent increase in case reports as well as an extensive growth in the manufacture, distribution, transportation, and international trade in fake medicines [5].

Any kind of medications that are in high demand by consumers and with profitable market prospects are targets for counterfeiting [6]. Due to the potential for huge profits in their markets, Europe (especially the United Kingdom) and the United States, have recorded an increase in seized counterfeit therapeutics, mostly facilitated by Internet transactions [5, 7]. As a result of the increasing demand for cheap medicines and low production cost, counterfeit pharmaceutical trade continues to be a massively lucrative business with sophisticated global networks. For instance, in a global crackdown by Interpol [8], about “\$41-million haul of illegal pharmaceuticals being sold online” were confiscated, with 9.9 million doses of counterfeit drugs seized in the United Kingdom [7] as reported by the Medicines and Healthcare Products Regulatory Agency (MHRA). Fake medications advertised for treatment of erectile dysfunction, hair loss and slimming (weight loss) were the frequently encountered drugs in the seized hauls. The United Nations Office on Drugs and Crime (UNODC) recognizes counterfeit medicines as a global public health threat [9] with a projected sale of approximately \$200 billion in 2013 [10, 11].

Typically adulterated medicines with extensive global reach include those for sleeping disorders [12], non-steroidal anti-inflammatory drugs, antibiotics [13–15], anticancer drugs [16, 17], erectile dysfunction drugs [18, 19] and anorectics [20–22]. Anorectics (or anorexics) refer to medicines or dietary supplements used for weight-loss purposes [23]. Medicines sold over-the-counter and from Internet sources adulterated with anorectics and/or their analogues or metabolites have been reported [24–29]. Similarly, phytotherapeutic (i.e., plant-based) formulations that are deemed “natural product” alternative treatment for obesity have been demonstrated to contain non-declared anorectics and adjuvants that boost their efficacy [24, 30–35]. There are, however, scarce reports that systematically review data from a forensic perspective. This paper, therefore, explores the current evidence related to anorectics in counterfeit weight-reducing formulations, including their forensic profiling, analytical techniques and legal status.

## Collection of the literature

Literature search, data selection and extraction were performed in Scopus, Web of Science and PubMed databases (2000–2019) for relevant peer-reviewed original articles. The search terms used were ‘counterfeit drugs’, ‘weight loss drugs’, ‘weight-reducing drugs’, ‘slimming drugs’, ‘anorectic agents’, and ‘counterfeit anorexics’. Google Scholar database search was used as an additional screening of initially identified publications to expand the source of data as well as to ensure the completeness of the search strategy. Current legislation on the anorectics was obtained from online portals/repositories of international statutory bodies and country-specific agencies.

## Anorectics in counterfeit weight loss products

An anorectic or anorexic is a general term used to describe any agent, such as drugs, medicines and/or dietary supplements, which is used for weight loss purposes. For instance, de Carvalho et al. [25] reported that about 80% of amphetamines produced legally are utilized for weight loss therapies. A significant factor that has accounted for the recent rise in anorectic use is obesity [36]. This condition, considered as a global public health problem [37], affects millions of individuals. Since medications for management and treatment of obesity are mostly prescription only in many countries [38], online pharmacies and unreliable Internet sources serve as an off-prescription route to purchase slimming products [22, 39]. Also, misleading advertisements, entrenched by the modern craze for the “ideal figure” beauty standards propagated by the mainstream media have contributed to unbridled view and quest of people for slimming products [3]. Counterfeiting contravenes the legislations of many countries [1, 40], because such formulations tend to have constituents inconsistent with their real declared and registered ones. The presence of these falsely declared active anorectic ingredients, therefore, makes their effects on human body random and unpredictable [32]. Apart from the adverse health effects and deaths associated with the toxic additives, such counterfeiting poses threats to pharmaceutical industries, as well as the economy and health care systems of countries [2, 10]. Moreover, the unpredictability regarding the chemicals that can be present as undeclared constituents of fake formulations requires the development of sensitive and selective analytical methods for their identification and quantification.

Anorectics agents found as adulterants in drugs, medicines and/or dietary supplements induce loss of appetite,

minimize intestinal fat (lipid) absorption as well as increasing the sensing of satiety [24]. Although there is a category of specifically designed drugs called anorectics (e.g., phentermine) mainly for the management of obesity, several other drug classes, mostly centrally acting ones, such as the amphetamines and similar sympathomimetic amines, have anorectic properties. The pharmacokinetics of important anorectic agents (Fig. 1) commonly encountered as adulterants in counterfeit drugs are discussed here.

### Sibutramine

Sibutramine (*N*-(1-(1-(4-chlorophenyl)-cyclobutyl)-3-methylbutyl)-*N,N*-dimethylamine hydrochloride) (trade names Meridia® in the USA, Reductil® in Europe and Australia), an amphetamine derivative, is an anorectic drug, which acts by inhibiting serotonin (5-hydroxytryptamine: 5-HT), norepinephrine, and to a small extent, dopamine reuptake [41–43]. Following the inhibition of these neurotransmitters, an enhanced sense of satiety and decrease in appetite, lead to reduced food intake [44]. Through thermogenic effects in basal and fed state, sibutramine and its two pharmacologically active metabolites, *N*-monodesmethyl and *N*-di-desmethyl sibutramine, have also been reported to increase energy expenditure [45–49]. Weight loss is as a result of the antiatherogenic effect of sibutramine, which enhances insulin resistance, metabolism of glucose, and dyslipidemia. Sibutramine is a routine adulterant in slimming products, especially in phytotherapeutic (herbal) food supplements [18, 24, 35].

### Fenfluramine

Fenfluramine (ethyl({1-[3-(trifluoromethyl) phenyl] propan-2-yl}) amine) is another anorectic associated with counterfeit slimming pharmaceuticals. Like sibutramine, it is also an amphetamine derivative and a serotonin reuptake inhibitor. It was mainly prescribed for the management of obesity [50]. The drug and its metabolites/analogues (dexfenfluramine, *N*-nitrosfenfluramine) act by affecting the brain's metabolism such that serotonergic transmission is enhanced in the hypothalamic feeding and satiety centres leading to reduced calorie intake [51]. Fenfluramine and its analogues are major synthetic chemicals found as adulterants in counterfeit weight loss medicines, with reported severe pulmonary hypertension and deaths [22, 52].

### Metformin

Metformin (1-carbamimidamido-*N,N*-dimethylmethanimidamide hydrochloride) is a biguanide antihyperglycemic drug used to manage type 2 diabetes [53]. It is pharmacologically different in action to other classes of antihyperglycemic

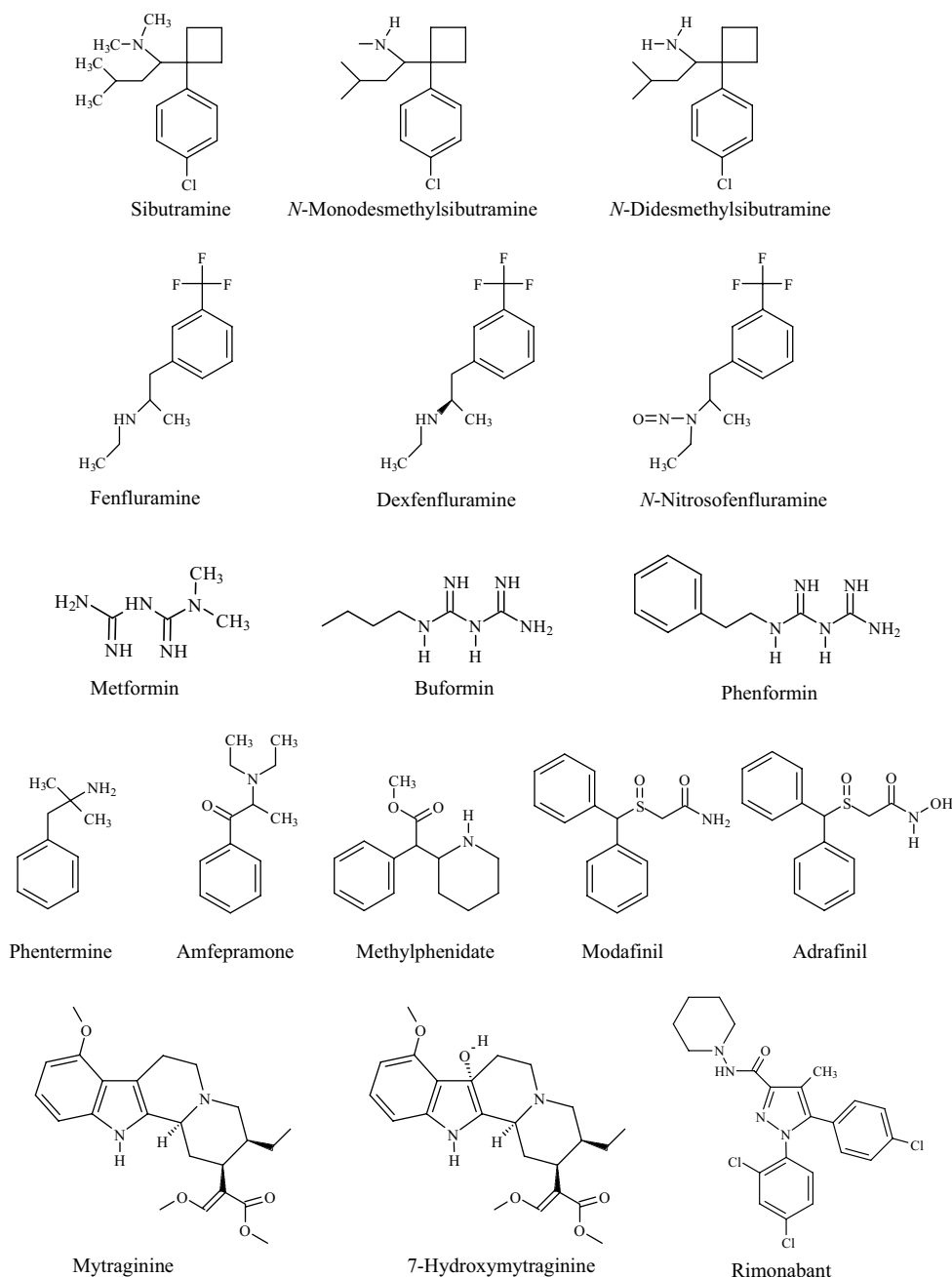
agents. It enhances glucose tolerance in type 2 diabetic patients by reducing hepatic glucose production, lowering intestinal absorption of glucose, increasing peripheral glucose uptake and improving insulin sensitivity [54–56]. Metformin is continuously detected in fake slimming formulations [57], because unlike sulfonylureas, it does not cause hypoglycaemia nor hyperinsulinemia even when administered alone in healthy subjects or patients with type 2 diabetes [58]. In some instances, however, metformin, like its withdrawn structural analogues buformin and phenformin, is known to cause lactic acidosis as a result of the very minimal liver uptake of serum lactate which is a required substrate of gluconeogenesis [59, 60].

### Phentermine

Phentermine ( $\alpha,\alpha$ -dimethylphenethylamine), traded under brand names Adipex, Adipex-P, Fastin, Lonamin, Phentercot, Phentride and Pro-Fast [61–64] is the oldest and commonest anorectic prescribed for the management of obesity [65]. It is a noradrenergic sympathomimetic agent approved by the FDA for short-term (< 12 weeks) treatment in combination with regular exercise and reduction in caloric diet, for the treatment of obesity [66]. However, phentermine has been used off-label as a long-term treatment for obesity without any serious adverse effects [67]. Initially ascribed as a central nervous system stimulant which triggers the release of norepinephrine in the hypothalamus [68], recent evidence suggests that phentermine inhibits the reuptake of norepinephrine and dopamine [68]. Subsequently, this suppresses appetite [69] and decreases body weight by reducing food intake and increasing resting energy expenditure [70, 71]. Phentermine is a key synthetic drug often illegally added to herbal slimming formulations and nutraceutical supplements [72, 73] to boost their efficacy. The use of this anorectic in such formulations has been associated with some adverse cardiovascular effects, such as primary pulmonary hypertension, palpitations, tachycardia, ischemic events [69], and dry mouth.

### Amfepramone (diethylpropion)

Amfepramone (2-diethylaminopropiophenon) stimulates the central nervous system to suppress appetite by increasing the release of catecholamines (dopamine and noradrenaline) in the hypothalamus and further limits their reuptake [74]. Subsequently, the drug is used as a short-term anorectic agent for the treatment of obesity [75]. Amfepramone is the most frequently abused and illicitly trafficked pharmacological adulterants in herbal weight loss products worldwide [32]. De Carvalho et al. [76] detected levels of amfepramone in all 106 herbal weight loss products analyzed. Similarly, Almeida et al. [77] found amfepramone as an adulterant in



**Fig. 1** Structures of anorectics frequently found in counterfeit weight loss formulations

herbal weight loss products at levels of 5% in 20 samples examined. Nonetheless, amfepramone has been associated with some moderate adverse effect, such as dry mouth, insomnia, anxiety, irritability, constipation, headache, dizziness and polydipsia [78]. The anorectic was previously linked to the development of pulmonary hypertension [79], but has since been disproved [80].

### Methylphenidate

Typically sold under the label Ritalin, methylphenidate is a central nervous system stimulant initially utilised as an analeptic for reversal of barbiturate-induced coma [81]; however, it is currently used to treat attention-deficit hyperactivity disorder (ADHD) [82]. Methylphenidate promotes

the release of stored or newly synthesized dopamine and inhibits reuptake by binding to the dopamine receptor [83]. This results in increased extracellular dopamine levels that facilitate slimming via suppression of appetite [81] as demonstrated by the sudden weight loss in ADHD patients [84]. The stimulant has been shown to increase blood pressure with the attendant risk of cardiovascular disease and strokes [85]. The seemingly explosive increase in prescriptions of Ritalin [86] could result in the medicine being abused as a weight-loss drug [87], and such incidence has been reported on a limited scale [87].

### Modafinil

Modafinil and its analogue have been detected in various slimming herbal products. Deconinck et al. [88] identified modafinil at a concentration of 0.125–1.00 mg/mL in herbal slimming products. Vanhee et al. [89] reported the presence of adrafinil, an analogue of modafinil in a food supplement that was submitted by the Federal Agency for Safety of the Food Chain (FASFC), Belgium. As a eugeroic psychostimulant, modafinil (2-[(diphenylmethyl) sulfinyl] acetamide) sold under the brand name Provigil, is used primarily for the treatment of narcolepsy, shift work sleep disorder and obstructive sleep apnoea [90–93]. While the exact mechanism is unknown, stimulating the release of norepinephrine, dopamine and serotonin and subsequently inhibiting their reuptake has been mooted [94]. Research by Makris et al. [95] reported improved appetite suppression following administration of modafinil and recommended its use for the treatment of obesity. Despite a lower risk of cardiovascular-related adverse effects, the drug has been associated with moderate side effects, such as headache, nausea, diarrhoea, nervousness, anxiety, dyspepsia, and insomnia [96, 97]. Recent works by Lazenka et al. [98] and Avelar et al. [99] have, however, shown that modafinil's action on brain's dopamine centres is identical to that of methamphetamine and cocaine.

### Rimonabant

Rimonabant, sold under the trade name Acomplia or Zimulti is an anorectic, antiobesity drug. It is a selective endocannabinoid CB<sub>1</sub> receptor antagonist that effects weight loss through the reduction in appetite [100]. In mature patients with type 2 diabetes, the drug showed some beneficial effects, such as glycemic control, reduced waist circumference and weight. However, rimonabant has since been withdrawn from the market and clinical use due to its neuropsychiatric side effects, notably, the onset of suicidal tendencies in patients [101]. Subsequently, analogues taranabant and otenabant, considered as a promising treatment for obesity due to improved anorectic effects were discarded [102].

Despite the risk of significant adverse effects, ample evidence indicates the availability of Acomplia, either genuine, counterfeited or as adulterants in weight loss formulations, to purchase on the Internet [103].

### Mitragynine

Mitragynine is obtained from the plant *Mitragyna speciosa* (also known as kratom) and is the most abundant active alkaloid isolated from the plant, with speciogynine, paynantheine, and 7-hydroxymitragynine making up the other essential alkaloids [104]. Kratom is primarily available as a drug of abuse, and its pharmacological effects have been reported to be dose-dependent [105]. Stimulant effects and opiate-like effects are achieved in lower and higher doses, respectively [106, 107]. Several adverse effects have been documented to be associated with mitragynine use in humans. These include dry mouth, constipation, changes in urination pattern, vomiting, nystagmus, tremor, anorexia and weight loss [108]. Anorexia and weight loss are side effects which are most prominent in chronic users of the drug [109], and this observation has influenced the use of mitragynine—a psychoactive plant extract—as an anorectic [110]. An online market [111] that sells extracts of kratom with different levels of purity and/or enhancement, for instance, declares “there are some detractors who consider kratom's long-term effects of weight loss to be an unwanted side effect” on the website in a concerted effort to advertise and encourage the use of mitragynine for slimming purposes among other “modern benefits”.

### Other drug classes

Apart from conventional anorectics, adulterants mainly found in fake slimming products have been grouped into five pharmacological classes, namely anxiolytics, diuretics, antidepressants, laxatives and other stimulants [88]. These drug groups are mainly utilized as coadjuvants in the formulations to possibly increase bioavailability or to minimize the various side effects, such as irritability, headaches, nervous depression, chemical dependence and unstable humour [52], associated with the use of certain anorectics to mostly mask the presence of anorexics.

Anxiolytic action of benzodiazepines, such as diazepam and alprazolam, routinely found in counterfeit slimming formulations is targeted at reducing the anxiety side effects caused by anorexics [112]. Antidepressants are a routine find in fake slimming pharmaceutical formulations. While they are mostly incorporated to counter the detrimental effects of the actual anorectics [25], some antidepressants directly facilitate weight loss. For instance, bupropion, a norepinephrine and dopamine reuptake inhibitor is an atypical antidepressant that causes the most weight loss

[113, 114] and frequently encountered as an adulterant in slimming formulas. However, the slimming action of this drug has been attributed to its side effects, mainly loss of appetite, nausea, and vomiting [115]. The FDA has, thus, approved bupropion for weight loss [116]. Sertraline is another antidepressant used as coadjuvant in fake slimming products since it has been documented to effectively limit the nervous depression most often reported in obese people using anorectics [25]. Tricyclic antidepressants, such as amitriptyline, trimipramine, imipramine and desipramine, selectively inhibit the reuptake of norepinephrine and to some extent, aid in the loss of weight due to this activity [117]. Diuretics (e.g., furosemide) and laxatives (e.g., phenolphthalein) are intentionally added adulterants to increase urine flow and intestinal motility, respectively. These synthetic compounds are often found as adulterants in herbal-based (phytotherapeutic) weight loss formulas [118], but their effect is not associated with a reduction in body fat but mainly increased loss of body water content. Many compounds from plant-based medicines have intrinsic laxative as well as diuretic properties and produce their deleterious effects akin to those from synthetic ones [119]. Therefore, the presence of undeclared laxatives or diuretics in phytotherapeutic carries risks, including dehydration and electrolyte imbalance [120], either independently or as a result of interaction with other constituents within the formulation.

Coffee, tea, guarana or other plant extracts have been reported to be efficient in loss of weight processes owing to caffeine consumption [121, 122], although some studies suggest that in-depth research should be performed to demonstrate the usefulness of these extracts or pure caffeine as food supplements for individuals who are following a diet [123]. Caffeine is metabolized to 3,7 dimethylxanthine (theobromine), 1,7 dimethylxanthine, and 1,3-dimethylxanthine (theophylline) by the liver, and the elimination mechanism depends on the initial dose of caffeine ingested.

## Legal status

The legal status of anorectics is mostly determined based on studies that evaluate the safety, tolerability, pharmacokinetics and/or toxicological profile/clinical outcome following the administration of a drug. For instance, due to the risk of heart failure, stroke and psychosis [124], sibutramine was banned in the United States by the Food and Drug Administration (FDA) [125], the European Union by the European Medicine Agency (EMA) [126], and Australia's Therapeutic Goods Administration (TGA) [127]. The ban was based on the data from the six-year Sibutramine Cardiovascular Outcome (SCOUT) trial with 10,742 patients which confirmed an increased risk of major cardiac events with the anorectic

use [128]. Subsequently, many countries have withdrawn sibutramine from their markets since 2010. Similarly, fenfluramine was banned and withdrawn from the market by the FDA in 1997 [129] due to its association with rare heart-valve disease in people who administered them as a diet pill [51]. Although the European Commission banned fenfluramine and dexfenfluramine based on "unacceptable safety profile in normal conditions of use, their lack of therapeutic efficacy and the consequent unfavourable risk/benefit balance" [130], the decision has since been revoked by the EU's General Court [131].

Due to concerns of the potential for abuse, phentermine has been classified as Schedule IV controlled substance [132]. Rimonabant, including analogous centrally acting weight-reducing drugs, was banned by the FDA following the emergence of severe mood disorders [133]. Neither *Mitragyna speciosa* nor its alkaloids fell under any listed schedules of the United Nations Drugs Convention [134, 135]. Some EU member states, however, categorize kratom as controlled, narcotic or "drug of concern" [134] while the US FDA has temporarily placed mitragynine and 7-hydroxymitragynine under Schedule I of the Controlled Substances Act [136], given its direct link with death [137]. Mitragynine is, however, banned in Malaysia, Myanmar, and Australia [138]. The current legal status of the main anorectics examined in this paper is presented in Table 1.

## Detection of anorectics in counterfeit slimming products

Differentiation between known authentic and suspected counterfeit formulations primarily involves physical examination and comparison of features on the drugs and packaging, such as texts on blister packs, packets and leaflet inserts [139]. This process is subjective and depends mainly on the experience of the analyst. Moreover, advancements in technology, which has contributed to sophistication in counterfeiting, mean that a careful visual inspection is inadequate for the purpose and must be followed by chemical analytical methods. Several methods and technologies are available for the screening of suspected counterfeit pharmaceutical formulations. For instance, marking and coding of medicines and/or their packaging are increasingly being undertaken by manufacturers, to check counterfeiting in efforts to protect their brand as well as to facilitate effortless initial examinations by law enforcement personnel [140]. However, following the discovery of a case of drug counterfeiting, it is prudent to obtain information on its chemical composition to enable assessment of potential dangers to patients or users.

For instance, an analysis of the FDA's "tainted weight loss products" [141] list, which consists of over-the-counter (OTC) products frequently advertised as dietary supplements

**Table 1** Legal status of selected anorectics in counterfeit formulations

Anorectic	Legal status	Reference(s)
Sibutramine	Banned and withdrawn from markets due to the risk of major cardiac events	[125–127]
Fenfluramine	Removed from the market by the manufacturer due to association with serious health problems	[142]
Phentermine	Schedule IV in the US, available by prescription only in many countries	[132]
Metformin	Available by prescription only in many countries	[143]
Buformin	Never approved for sale in the US, removed from markets in most countries due to increased risk of lactic acidosis. Available by prescription only in Romania <sup>1</sup> , Hungary <sup>2</sup> , Taiwan <sup>3</sup> and Japan <sup>4</sup>	[144, 145] <sup>1</sup> , [146] <sup>2</sup> , [147] <sup>3</sup> , [147] <sup>4</sup>
Phenformin	Withdrawn from the market as an antidiabetic drug due to the high risk of fatal lactic acidosis	[148]
Rimonabant	Never approved in the US, withdrawn from the market globally due to concerns over dangerous psychological side effects, including suicidality and depression	[101, 133]
Amfepramone (diethylpropion)	Classified as Schedule IV controlled substance in the US and Canada <sup>1</sup> , Class C drug in the UK <sup>2</sup> , and available by prescription only in Australia <sup>3</sup> and Germany <sup>4</sup>	[149] <sup>1</sup> , [150] <sup>2</sup> , [151] <sup>3</sup> , [152] <sup>4</sup>
Methylphenidate	Designated Schedule II internationally <sup>1</sup> , the US <sup>2</sup> , Schedule III in Canada <sup>3</sup> and Schedule 8 in Australia <sup>4</sup> . Controlled substance Class B in the UK <sup>5</sup> , Class B2 in New Zealand <sup>6</sup> , List II controlled substance of medical value in Sweden <sup>7</sup> , and controlled Psychotropics in Japan <sup>8</sup>	[153] <sup>1</sup> , [154] <sup>2</sup> , [155] <sup>3</sup> , [156] <sup>4</sup> , [157] <sup>5</sup> , [158] <sup>6</sup> , [159] <sup>7</sup> , [160] <sup>8</sup>
Modafinil	Classified as Schedule IV controlled substance in the US <sup>1</sup> and Sweden <sup>2</sup> , Schedule 4 prescription-only medicine in Australia <sup>3</sup> , Class I and Schedule 1 psychotropic drug in China <sup>4</sup> and Japan <sup>5</sup> , respectively, and Schedule II controlled substance in the same class as morphine and cocaine in Russia <sup>6</sup>	[149] <sup>1</sup> , [161] <sup>2</sup> , [162] <sup>3</sup> , [163] <sup>4</sup> [160] <sup>5</sup> , [164] <sup>6</sup>
Mitragynine (plant / alkaloids)	Not listed under any schedules of the UNDC <sup>1</sup> ; not approved for any medical use and under Schedule I consideration in the US <sup>2</sup> , controlled as Narcotic in Australia <sup>3</sup> and New Zealand <sup>4</sup> ; controlled as Designated substance in Japan <sup>5</sup> . Plant controlled in Europe <sup>6</sup> and prohibited in the UK <sup>7</sup>	[134] <sup>1</sup> , [165] <sup>2</sup> , [162] <sup>3</sup> , [166] <sup>4</sup> , [167] <sup>5</sup> , [110] <sup>6</sup> , [168] <sup>7</sup>

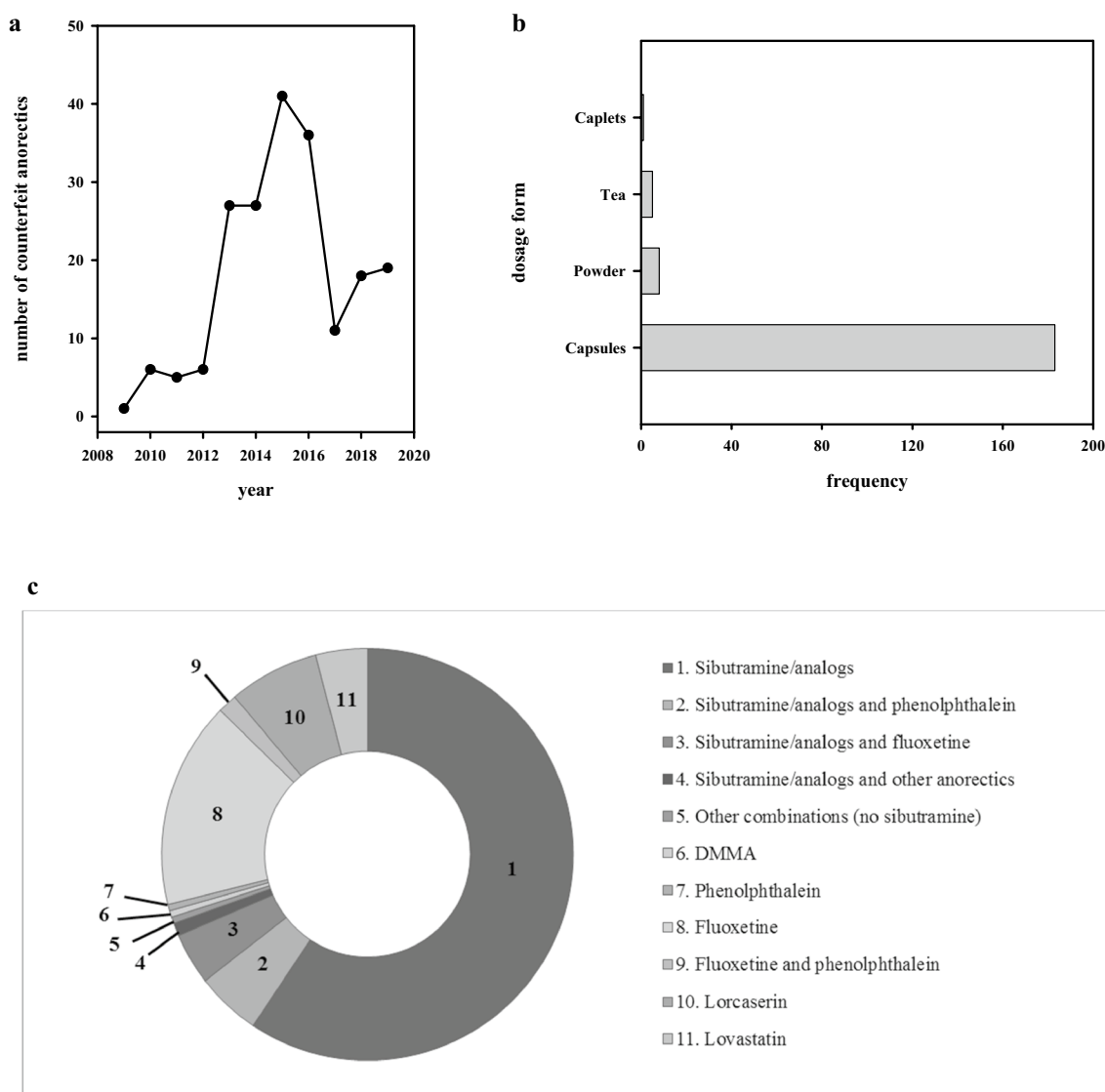
but containing potentially harmful undeclared active ingredients, gives insight to the need for robust detection of counterfeit anorectics. The eleven-year data, presented in Fig. 2a, shows an extensive number of adulterated anorectics on the market (total 197), with an average of 18 adulterated new products per year. Multiple drug classes of banned and legal (prescription only) anorectics were deceptively hidden in these products. Predominantly, either sibutramine or its analogues only (59%) or in combination with other drug classes (84%) are found as undeclared chemicals in OTC slimming products (Fig. 2c). Most of these fake slimming medicines are developed for oral administration, commonly as capsules (Fig. 2b).

Due to the broad range of synthetic pharmaceutical classes that may be found as adulterants in slimming formulations, selectivity and sensitivity form the essential

analytical requirements that must be fulfilled. Determination of chemical constituents of a suspected fake formulation, therefore, requires the vital initial step of sample preparation (extraction) and preconcentration using various techniques.

### Sample preparation for anorectics in counterfeit pharmaceuticals

Despite the major advancements and production of powerful analytical instruments (e.g., sensors, microscopy, chromatography, spectroscopy), direct sample analyses, especially in biological and pharmaceutical formulations samples are often not possible owing to factors, such as matrix interference and low analyte concentrations [169]. This necessitates the use of some pretreatment steps aimed at sample



**Fig. 2** Counterfeit over-the-counter (OTC) weight loss products reported in the US following FDA laboratory analysis. **a** Tainted anorectics reported in the US from April 2009 to December 2019. **b** Distribution of common dosage forms of OTC weight loss products

in the US. **c** Undeclared pharmaceutical active ingredients detected in OTC weight loss products in the US [see supplementary material, Table S1]. *DMMA* 3,4-dimethoxy-*N*-methylamphetamine

cleanup, enrichment, as well as signal enhancement. Notable (but not exhaustive) pretreatment methods that have found application in preconcentration and cleanup of analytes prior to instrumental analysis in forensic investigations include: filtration with polyvinylidene difluoride membrane syringe [26, 27, 103], polytetrafluoroethylene [24] or cellulose acetate [170] filter following sample dissolution in organic solvent and sonication; solid-phase extraction (SPE) [171]; liquid–liquid extraction (LLE) [28], microwave-assisted extraction (MAE) [172], liquid-phase microextraction (LPME) [173, 174] and solid-phase micro-extraction (SPME) [175].

Sporkert and Pragst [176] used headspace SPME (HS-SPME) to extract amfepramone and other organic compounds. HS-SPME offers enhanced purification for complex biological samples, ensures green chemistry by avoiding organic solvent use and efficiently couple with gas chromatographic systems. Notwithstanding, the recoveries achieved by the HS-SPME pre-concentration technique were unsatisfactory. Other extraction methods also suffer significant limitations. SPE, especially, suffers analytic breakthrough when a large volume of samples is analysed [177]. Though being relatively simple, miniaturised and fast, LPME and SPME techniques are constrained with sample carry-over,



relatively high cost, the fragility of the fibre and relatively low accuracy [178, 179]. Given these limitations, developing new techniques with improved speed, safety, sensitivity, and reliability is of significant analytical interest. There is currently no consensus on a specific extraction/pre-concentration method for anorectic sample preparation. The different methods available in literature reflect the complexity of such counterfeited formulations and the target analytes.

## Analytical methods for determination of counterfeit anorectics

Undeclared chemicals in slimming products or bodily fluids (such as blood or urine following exposure) can be analytically determined using several conventional methods. The most significant detection, identification and quantification of the parent drugs, analogues and/or metabolites are, however, achieved utilising the established techniques of liquid chromatography (LC) and gas chromatography (GC) coupled with mass spectrometry (MS) and spectroscopic methods. Table 2 shows cases of weight loss formulation use, analytical determination techniques and clinical outcomes.

### Liquid chromatography–mass spectrometry

Liquid chromatography, coupled with mass spectrometry detection (LC–MS) has emerged as the preferred technique for identification and quantification of chemical entities in counterfeit and illegal pharmaceutical preparations [27, 180]. Considering the analytical gold standard, the LC–MS has been extensively utilized due to the high separation power that facilitates application to complex mixtures, enhanced sensitivity and specificity without the need for derivatization, and it is currently a well-established presence in most laboratories worldwide for routine analyses. Following separation via LC, the MS primarily enables conversion of analyte molecules to an ionized state, separating charged molecules according to their mass-to-charge ratio ( $m/z$  value) and subsequent identification as the charged species [181]. The foregoing thus enables targeted and untargeted screening of formulations, and in some instances, identification and/or structural elucidation of constituents of an unknown compound, when LC–MS is linked with infrared (IR) and nuclear magnetic resonance spectroscopy techniques [182].

Ultra-performance liquid chromatography (UPLC) provides a meaningful improvement over conventional LC and is especially useful for method development [170], where quick run times, including rapid response to alterations in column and mobile-phase conditions, are required. When linked to MS, UPLC is time-saving, offering improved performance in resolution, sensitivity and precision [183, 184]. Stypulkowska et al. [185] utilized LC–MS to determine the

sibutramine and its analogues in some herbal dietary supplements. Similarly, undeclared rimonabant, sibutramine and their respective analogues were identified in imitated Acomplia [103]. In a survey of twenty-two herbal slimming preparations, Wang et al. [34] developed an LC–MS method which facilitated the simultaneous determination of sibutramine (45.5%), *N*-monodesmethyl sibutramine (9.1%) and phenolphthalein (13.6%) in the samples analysed.

Liquid chromatography with tandem mass spectrometry (LC–MS/MS) has been applied for analytical profiling of counterfeit pharmaceuticals in recent years. By coupling LC and two MS connected in series, the method allows sample separation, ionization and characterization utilizing the  $m/z$  value and relative abundance [186]. Subsequently, LC–MS/MS enables analysis of complex matrices with optimum molecular specificity and detection sensitivity that allow structural identification of each constituent of the mixture [187]. Kim et al. [188] developed and validated an LC–MS/MS method for routine herbal dietary supplement adulteration screening for sibutramine and its metabolites. An LC–MS/MS method with the ability to screen synthetic adulterants from multiple pharmacological classes including anorectics (e.g., fenfluramine, methylphenidate, sibutramine) in herbal remedies was also developed by Bogusz et al. [189]. A similar technique applying LC–QTRAP–MS/MS was used by Chen et al. [190] to determine blood pressure and lipid-lowering agents, sedative drugs, antidiabetic drugs, weight-reducing agents and aphrodisiac compounds, in adulterated plant-based health supplements. Other analytical approaches to the analysis of counterfeited slimming phytotherapeutic formulations have been comprehensively reviewed by De Carvalho et al. [25].

### Gas chromatography–mass spectrometry

The GC method has been used in the detection and characterization of counterfeit medicines. When combined with mass spectrometry, GC–MS primary use lies with the analysis of illegal pharmaceutical formulations in medicine control laboratories [32]. For example, GC–MS was utilized to determine anorectics, stimulants and benzodiazepines in counterfeit slimming drugs [32, 112]. Due to the nonvolatile and considerable hydrophilic nature of most pharmaceutical formulations, complex derivatization to their respective less polar compounds is often necessary to enhance their identification and quantitative analysis [169]. GC–tandem MS (GC–MS/MS) offers enhanced separation, higher precision and selectivity, and has been employed in profiling some anorectics in fake pharmaceuticals. Li et al. [191] developed a GC–electron ionization–MS/MS method to simultaneously detect seven adulterants, including the anorectics fenfluramine, amfepramone and sibutramine in slimming functional foods. In a recent study, and the first proof of concept,

**Table 2** Cases of anorectic adulterants in counterfeit weight loss formulations, clinical outcomes and analytical determination aligned chronologically

Reference	Formulation and adulterants detected	Case	Clinical features	Extraction method	Analytical method	Outcome
Hughes (2019) [206]	Mitragynine	A 27-year-old man consumed quetiapine and mitragynine	Autopsy examination revealed dark fluid emanating from the mouth and intramuscular haemorrhage on cut sections of the tongue	N/A	HPLC	Death
Alshaikhi et al. (2018) [207]	Herbal slimming product 'Burning Fat Slimming Capsule' obtained from the Internet Sibutramine	A 29-year-old woman was hospitalised 2 months after the ingestion of slimming product	Agitation and psychosis, nervousness, insomnia, hyperactivity, and obsession	N/A	HPLC	Treated and discharged
Bunya et al. (2017) [208]	Thai-made weight loss capsule and tablets called "Hospital diet" bought on the Internet Sibutramine, hydrochlorothiazide, bisacodyl, chlorpheniramine, and a thyroid hormone	A 21-year-old woman, found unresponsive on a sidewalk, after taking only one day's dose of weight loss pills from Thailand	Ventricular fibrillation with agonal breathing. Lack of response after 4 defibrillation attempts. Spontaneous circulation achieved 30 min after administering extracorporeal membrane oxygenation	N/A	N/A	Patient placed in intensive care. Automated cardioverter defibrillator implanted on day 42 and discharged on day 51 Clinical data excluded any other underlying pathology, including congenital causes
Shapira et al. (2016) [209]	Dietary supplements "One Slim" and "Amana Care" purchased from a local pharmacy Sibutramine, phenolphthalein	A 26-year-old female admitted to emergency after ingestion of slimming dietary supplements for two weeks prior	Visual hallucinations, abnormal behaviour, hyperkinesia, tachycardia, dizziness, facial flushing	N/A	N/A	Patient responded well to haloperidol therapy and discharged
Gunaydin et al. (2015) [210]	Herbal slimming product 'La Jiao Shou Shen' bought on the Internet Sibutramine	A 17-year-old female was admitted to the emergency department for the ingestion of weight loss products	Palpitation, dizziness, fatigue, and insomnia	N/A	N/A	Treated and discharged
Vecchio et al. (2014) [211]	Herbal slimming product collected from patients Metformin	The study involved 66 patients hospitalised at the Pavia Poison Center from 2007 to 2011 for using metformin as a therapeutic agent for the management of type II diabetes	Mild gastroenteritis, neurological impairments, respiratory failure, hemodynamic disorder, acute heart failure, sepsis, severe pneumonia, post-surgical shock, lactic acidosis, and acute renal failure	N/A	HPLC	17 deaths. Others treated and discharged
Zhu et al. (2014) [57]	Metformin	12 samples from anonymous real cases	N/A	N/A	LC-MS/MS	N/A

Table 2 (continued)

Reference	Formulation and adulterants detected	Case	Clinical features	Extraction method	Analytical method	Outcome
Khazan et al. (2013) [212]	9 herbal slimming products bought from the market Phencyclidine	20 women using Chinese herbal slimming products were recruited for the study during spring 2010 in Iran	Dry mouth, hand tremor, increased blood pressure, tachycardia, arrhythmia, anxiety, diarrhoea, sleep disturbances, decreased appetite, euphoria, feeling hyper, and palpitations	N/A	Immunochromatographic assay	All 20 women declared their willingness to continue to use these products despite the reported side effects
Heo and Kang (2013) [213]	Non-prescription weight loss formulation called “Slim-30” <i>N</i> -Desmethyl sibutramine	A 32-year-old male admitted with progressively worsening dyspnoea on exertion following continued use of unauthorised slimming pills for 7 months	High blood pressure, palpitation, pitting oedema in lower extremities, dilated cardiomyopathy with massive intracardiac thrombus	N/A	N/A	Good clinical response to treatment. Discharged in a stable condition and prescribed a beta-blocker, angiotensin-converting-enzyme inhibitor, and oral warfarin. One-month follow-up was required
Lam et al. (2012) [214]	A slimming product obtained from the Internet Sibutramine, animal thyroid tissues, caffeine, and phenolphthalein	A 21-year-old woman was admitted at the hospital for overdose ingestion of an illicit slimming product. Patient had been taking this medicine for 4 years for weight loss	Coma, fever with persistent sinus tachycardia	N/A	HPLC–DAD, LC–MS/MS	Treated and discharged

Table 2 (continued)

Reference	Formulation and adulterants detected	Case	Clinical features	Extraction method	Analytical method	Outcome
Ching et al. (2012) [215]	Ku Le Kang, Yi Su Kang Jiao Nang, Jiang Tang Ning Jiao Nang, Xiao Ke Shu Ping – Jiang Tang Ning Jiao Nang, Tian Sheng Yi Bao, Tang Le Shi Shen Jiao Nang, Yi Zhi Ren Jiao Nang, Shen Ji Xi Jiao Wan, Ba Bao Xiao Ke Wan, Yi Huo Xiao Tang Ning Jiao Nang, Shen Shi Yi Huo Jiang Tang Ning Jiao Nang, Yi Dao Pai Du Jiao Nang, Jing Xue Wen Tang Jiao Nang, Tang Ke Wan	27 cases of clinical toxicities associated with the use of herbal PCMs	Heart failure, severe Lactic acidosis, Hypoglycaemia, Renal impairment	N/A	N/A	Treated and discharged
Tang et al. (2011) [22]	81 slimming products sourced from the internet, OTC, friends, local slimming centres, and herbalists Sibutramine, <i>N</i> -desmethylsibutramine, <i>N</i> -bisdesmethylsibutramine, phenolthalein, fenfluramine, <i>N</i> -nitrosofenfluramine, anthraquinones, bisacodyl, hydrochlorothiazide, animal thyroid tissue, spironolactone	66 cases of poisoning involving illicit slimming products between Jan. 2004 and Dec. 2009	Severe to moderate poisoning presenting with: Liver failure, supraventricular tachycardia, palpitations, tremor, insomnia, myocardial infarction, hypertension, generalized weakness, dizziness, sweating	N/A	HPLC–UV GC–MS or LC–MS/MS, microscopy, immunosay	One death. Others treated and discharged
Vitalone et al. (2011) [216]	The Italian National Surveillance collected samples of slimming pills from patients Fluoxetine, metformin, and levothyroxine	46 patients with adverse reaction due to ingestion of weight-loss products were admitted from April 2002 to June 2010	Ventricular fibrillation, vomiting, and abdominal problems	N/A	HPLC–UV, HPLC–FLUOR, and ion-exchange chromatography	All patients were treated and discharged

Table 2 (continued)

Reference	Formulation and adulterants detected	Case	Clinical features	Extraction method	Analytical method	Outcome
Chen et al. (2010) [52]	20 proprietary herbal slimming products (bought from internet & OTC) Sibutramine, <i>N</i> -desmethylsibutramine, <i>N</i> -bisdesmethylsibutramine, phenolthalein, fenfuramine, mazindol, hydrochlorothiazide, spironolactone, caffeine, emodin, aloe-emodin, physcion	16 patients hospitalised between Jan. 2004 to Oct. 2009 from taking herbal slimming formulation	Psychosis, auditory and visual hallucinations, persecutory ideas, suicidal ideation	N/A	HPLC (initial screening) GC-MS or LC-MS/MS	Patients treated and discharged (recovery time range from 3 days to 3 months)
Chong (2010) [217]	Herbal slimming pills Sibutramine, animal thyroid tissue, phenolphthalein, phentermine, paracetamol, oleanolic acid, caffeine, and <i>N</i> -bisdesmethylsibutramine	Two women aged 19 and 37 admitted with mania-like psychosis after taking non-prescription herbal weight loss pills	Sudden onset of paranoid ideations and self-harming behaviour, irritability, poor sleep, paranoid delusions, auditory and visual hallucinations	N/A	LC-MS/MS	Treated with quetiapine and Valproate (19 years old); and risperidone (37 years old) and discharged
Müller et al. (2009) [218]	Lida Dai dai hua, slimming capsule Sibutramine	17 cases of poisoning with a single product, said to be of purely herbal origin, that was bought over the Internet over 3 years in Göttingen and Freiburg	Malaise, tachycardia, headache, agitation, arterial hypertension, nausea, vomiting, dyspnoea, insomnia, left-sided chest pressure, elevated temperature, and, in two cases, psychosis	acidic hydrolysis and acetylation	GC-MS and HPLC-DAD	Treated and discharged
Yim et al. (2008) [219]	Herbal slimming capsules bought in mainland China Sibutramine	A 37-year-old woman admitted at the Accident and Emergency Department in Hong Kong for taking herbal slimming pills 3 days before her admission	Retrosternal chest pain, nausea, sweating, myocardial infarction	N/A	LC-MS	Treated and discharged

Table 2 (continued)

Reference	Formulation and adulterants detected	Case	Clinical features	Extraction method	Analytical method	Outcome
Poon et al. (2008) [220]	Two herbal weight loss product, Qing Zhi Mei and Chan Qing Chun, bought from a beauty salon and Over the counter Caffeine, anthraquinones, riboflavin, nicotinamide, pyridoxine, <i>N</i> -nitrosodifluoramine, fenfluramine, sibutramine, phenolphthalein, propranolol, ephedrine, and animal thyroid tissue	Three patients, a 53-year-old woman, a 41-year-old man, and a 38-year-old woman were admitted in 2005 after taking herbal slimming product	Pulmonary hypertension, moderate aortic regurgitation, and prominent right heart failure, pericardic paralysis. Patients showed factitious thyrotoxicosis	Uniform SPE	HPLC–DAD	Treated and discharged
Ching et al. (2008) [149]	Herbal-based PCM: Yi Su Kang Jiao Nang, Xiang Lian Pian, Ching Shin Bei Dou Gen Pian and Yan Suan Shiao Bo Jiao Pian, Ku Le Kang, Shiao Ke Shu Ping–Jiang Tang Ning Jiao Nang, and Huo Yi Jiang Tang Dan, bought OTC Phenformin, glibenclamide, rosiglitazone	Four older women (57–79 yr) and 2 older men (56 yr & 78 yr) with history of diabetes, defaulted follow-up of prescription and used PCM as alternative	Nausea, vomiting, hypoglycaemia, heart failure	Uniform SPE	LC–DAD, GC–MS and LC–MS/MS	Treated and discharged
Yuen et al. (2007) [29]	26 over-the-counter slimming products collected from 21 patients Sibutramine and its analogue, <i>N</i> -nitrosodifluoramine, nicotinamide, emodin, aloe-emodin, tiratricol, fenfluramine and its analogue, thyroxine, thyroid, mazindol, caffeine, hydrochlorothiazide, propranolol, dobutamine and phentermine	42 patients hospitalised between September 2004 to December 2006 at the Hospital Authority Toxicology Reference Laboratory for consuming slimming products	Fulminant hepatic failure, pulmonary hypertension, moderate aortic regurgitation, right heart failure, and generalised body weakness		GC–MS or LC–MS/MS	All patients were treated and discharged

Table 2 (continued)

Reference	Formulation and adulterants detected	Case	Clinical features	Extraction method	Analytical method	Outcome
Hung and Chang (2006) [221]	Weight loss pill collected from the patient Phentermine, chlorpheniramine maleate	A 23-year-old woman was admitted at the emergency department for taking slimming pills for 3 consecutive days	Cardiac arrhythmia, lethargy, headache, dizziness, nausea, vomiting, dyspnoea, and palpitation	N/A	N/A	Treated and discharged
Jung et al. (2006) [222]	A Chinese herbal weight loss product 'LiDa Dai Dai Hua Jiao Nang' bought from the Internet Sibutramine	A 20-year-old woman was admitted to the hospital for taking a Chinese herbal weight loss product for 6 days	Severe headache, vertigo, numbness	Methanol extraction, acid hydrolysis and methylation	GC–MS, HPLC–DAD	Treated and discharged
Lai et al. (2006) [223]	A Chinese slimming product (Shubao) bought from the West Midlands N-Nitrosofenfluramine	4 patients hospitalised for taking a Chinese slimming pill between November 2003 and June 2004	Severe acute hepatic injury	N/A	N/A	One patient received a liver transplant while the others fully recovered after discontinuing the herbal product
Hsiao et al. (2005) [224]	'60 DNP' capsules Dinitrophenol, caffeine, ibuprofen and acetaminophen	A 17-year-old female presented to the paediatric emergency department after ingesting diet pills 4 h prior	Vomiting, diaphoretic, tachycardia	N/A	UV/VIS	Death
Lau et al. (2004) [225]	39 capsules of Chinese dieting pills (Slim 10) were collected from the patients Fenfluramine, N-nitrosofenfluramine, nicotinamide, thyroxine	A 42 years old woman was hospitalised for consuming 4 bottles of dietary pills 'Slim 10' each containing 120 with only 39 capsules remaining at the time of her death	Acute hepatitis, severe jaundice, hepatic encephalopathy, coagulation, nosocomial sepsis, renal failure, and multi-organ failure	Methanol and dichloromethane	GC–MS, GC–MSD, GC–TEA, HPLC–DAD	Death
Adachi et al. (2003) [226]	2 dietary slimming products (Chinese herbal weight loss aids Chaso and Onshido) N-Nitrosofenfluramine	12 patients were hospitalised at Keio University Hospital and other hospitals in Japan between April to July 2002 after taking weight loss products	Fatigue, appetite loss, hepatic encephalopathy, acute liver injury and hepatic failure	N/A	LC–MSD	One death, 1 patient underwent a liver transplant and the condition of the 10 patients improved after discontinuing the use of the products
Nakadai et al. (2003) [227]	10 Chinese slimming products obtained from patients N-Nitrosofenfluramine, fenfluramine, dexfenfluramine	800 cases of liver damage were reported for taking Chinese diet aids in Japan from 2001 to summer 2002	Liver damage	N/A	NMR, GC–MS, HPLC	N/A

Table 2 (continued)

Reference	Formulation and adulterants detected	Case	Clinical features	Extraction method	Analytical method	Outcome
Corns and Metcalfe (2002) [228]	Herbal slimming capsules imported from mainland China: Ba Zhen Wan, Dan Gui Wan, Jiao Nang (Tiansu), Kang Gu Che Sheng Wan, Kintop, Qian Er, Shen Qi Da Bu Wan, Storm, Unnamed yellow tablets Fenfluramine	Three females (29, 41 and 46-year-olds) taken to the hospital after consuming weight loss formulations obtained from a herbalist	Hypertension, loss of weight, abdominal pain, rapid palpitation, nausea and visual hallucinations	N/A	GC-MS	Treated and discharged

*DAD* diode array detection, *GC-MS* gas chromatography–mass spectrometry, *HPLC* high-performance liquid chromatography, *LC-MS/MS* liquid chromatography–tandem mass spectrometry, *LC-MS* liquid chromatography–mass spectrometry, *LC* liquid chromatography, *N/A* not available (author(s) did not provide information in the article), *NMR* nuclear magnetic resonance spectrometry, *OTC* over-the-counter, *PCM* proprietary Chinese medicine, *SPE* solid-phase extraction, *SPE* solid-phase extraction, *UV* ultraviolet detection

Arbouche et al. [192] developed a GC–MS/MS method to determine metformin in human hair following prolonged use of the antidiabetic drug. The sensitive technique showed limits of detection and quantification at 1 and 100 pg/mg hair, respectively, but illustrated the poor incorporation of metformin into human hair in comparison with other drugs.

Derivatization for GC–MS analysis depends on the chemical properties of specific anorectics. For example, pentafluoropropionic anhydride derivatization was employed for simultaneous screening of fenfluramine and phentermine in urine samples [142]. Similarly, Strano-Rossi et al. [169] detected metabolites of sibutramine in a study of its pattern of fragmentation following derivatization to the corresponding methyl and trimethylsilyl derivatives. Arbouche et al. [192] and Goedecke et al. [193] used acylation reagent, *N*-methyl-bis(trifluoroacetamide) (MBTFA) derivatization and GC–MS to determine the metformin in hair and surface water, respectively. A similar GC–MS approach, in combination with LC–diode array detection, was used by Liu et al. [194] to screen anorectics and other adulterants in 266 phytotherapeutic formulations. Unlike LC–MS, the derivatization requirement of GC–MS analysis makes the analytical procedure cumbersome and error-prone [195]. Current trends in analytical method development and validation are aimed at advancing simplicity and reducing time at each analytical stage while increasing analytical throughput. The need to often change solvents increases complexity and extends sample preparation times. This makes GC–MS analysis process of counterfeit formulations inconsistent with current trends, despite its merits. However, the costs for GC–MS or GC–MS/MS instruments are relatively lower than those LC–MS/MS instruments at this time.

### Capillary electrophoresis

Capillary electrophoresis (CE) has become a versatile separation technique in contemporary biopharmaceutical analytics, albeit in a considerably smaller footprint as compared to GC and LC. Sample pre-concentration for CE allows for short analysis times, reduced volumes of the sample and reagents used, and high selectivity [196]. Two forms of CE, micellar electrokinetic chromatography [197] and capillary zone electrophoresis (CZE) [198] have been used as affordable alternatives for counterfeit pharmaceutical determination. Piette and Parmentier [199] utilised CZE to analyse amphetamine-based anorectics in seized formulations. While the conventional CE technique generally employs UV detectors, hyphenation with MS detectors for highly resolved chemical and structural information of adulterants of weight loss pills and dietary supplements have been investigated as a potential confirmatory approach. Akamatsu and Mitsuhashi [200] and dos Santos et al. [201] developed CE–MS/MS methods to identify anorectics and other adulterants in some



phytotherapeutics, yielding limits of detections lower than  $0.06 \mu\text{g L}^{-1}$ . As compared to LC, CE equipment and accessories are cheaper, lasts longer, simple to use and requires minimal amounts of reagents and samples [202]. Further method development and validations are envisaged to offer CE as a robust option in fighting counterfeit drugs especially in developing countries.

## Nanomaterials

Nanotechnology is a powerful tool that has demonstrated its usefulness in many fields, although more work needs still to be done to transfer the results from research to routine analysis. Nanomaterials are used in the dietary supplement industry to improve the drug delivery to target organs, tissues or cells. The methods used for the determination of nanomaterials in dietary supplements have been reviewed, finding that CE is the technique of choice to determine different metal nanoparticles, such as gold, platinum or palladium [203].

The second use of nanomaterials deals with their use in the proposal of new analytical methods for the determination of anorectics, although it is still in the incipient stage. Sample preparation is one of the most challenging steps since most errors in the analytical process arise from this step. Carbon nanotubes (CNTs) have been used to determine metformin [204] and amphetamine-derived anorectics, including phentermine [205].

Magnetic multi-walled CNTs were used to produce a methacrylate-based molecularly imprinted polymer on their surface, where metformin was used as the template [204]. Some advantages of this polymer are the faster kinetics of sorption and desorption owing to the high surface area of nanomaterials, as well as the ease of operation owing to the magnetic properties of the nanomaterial that facilitates its separation from complex matrices during the extraction process. The method was applied to different spiked samples, such as urine, human serum, and sea, tap and mineral water, with extraction recovery percentages in the range of 95.5–104.7%. Oxidized multi-walled CNTs have been used to coat SPME fibres for the microextraction of 7 amphetamine-like stimulants in urine [205]. The oxidation of CNTs allows a higher surface area compared to bare CNTs, as well as the introduction of hydroxyl groups owing to the oxidation process enhances the interaction with polar analytes.

The use of nanomaterials for the detection of anorectics has been more extensively used than for sample preparation. Although gold-based nanomaterials have been used for the determination of metformin alone [229] or in binary mixtures [230] and fenfluramine [231], the most important contribution of nanomaterials to anorectic determination is their integration into electrochemical sensors [232–234]. Several sensors have been described for metformin determination, as

amperometric sensors, using graphene/nanoflakes-polymethylene blue/fluorine doped tin oxide, nickel oxide nanotubes, nanostructured Fe-Cu/TiO<sub>2</sub>, a Cu metal-organic framework to modify surface of different electrodes [232], as well as zinc ferrite, copper oxide and gold nanoparticles have been successfully used to modify the surface of a glassy carbon electrode [233]. Impedimetric sensors have also been developed using nanomaterials, such as Prussian Blue nanocubes/carbon nanospheres/fluorine doped tin oxide. The excellent features of nanomaterials, such as high surface-to-volume ratio and high conductivity, have provided high sensitivity and selectivity levels to the developed sensors. Screen-printed electrodes have been integrated with CNTs to detect modafinil in saliva by adsorptive stripping voltammetry [234]. This constitutes one example on integrated analytical platform using nanomaterials and printing technologies, where CNTs are used as SPE sorbents prior to adsorptive stripping voltammetry. The integration of SPE and the printed electrochemical sensor constitutes a real advantage and ease the operation of the electrochemical sensor when the analysis of real samples is tackled.

## Conclusions

Slimming formulations doped with anorectic cocktails to boost their weight-reducing effectiveness are not uncommon and present a global health and safety threat. The effects of such additives, often from multiple chemical classes on the human body, are unpredictable. This review has highlighted the current scope of anorectics generally found as adulterants in weight-reducing formulations, including their mode of action and adverse effects on unsuspecting users. The limitations and mitigation strategies of conventional sample preparation / instrumental analyses have also been presented. While LC-MS(/MS) remains the gold standard for analytical profiling of such counterfeits, improved pre-concentration methods are required to facilitate rapid and quantitative identification of specific chemical constituents. Also, CE presents an essential alternative to LC and GC due to much lower cost in fighting anorectic adulteration in pharmaceutical formulations. The incipient use of nanomaterials has opened new insights in sensor development as a powerful tool to screen for samples before proceeding to confirmatory analysis by LC-MS, GC-MS and CE. This summary of available literature also provides insight into the present state of research in profiling adulterants in counterfeit anorectic products.

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## Compliance with ethical standards

**Conflict of interest** There are no financial or other relations that could lead to a conflict of interest.

**Ethical approval** This article does not contain any studies with human participants or animals performed by any of the authors.

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