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Review

Common risks of adulterated and mislabeled herbal preparations

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ABSTRACT

Due to the growing trend of returning to nature and the fear of adverse reactions from conventional medicines, people are increasingly resorting to the use of herbal preparations. Because of long-term use and natural origin these preparations give a sense of security. But herbal formulations also possess undesirable effects and, among other dangers, present a risk connected with deliberate addition of synthetic compounds, deliberate or unintentional replacement of the plant species or simply a risk of mislabeling. While the replacement of the plant species occurs in a very different groups of herbal products, reports of added illicit synthetic substances often include groups of herbal weight-loss preparations, sexual enhancers, preparations for treatment of rheumatic and inflammatory diseases, antidiabetic and blood pressure lowering preparations. In the world of Internet ordering, these are the dangers that everyone should be aware of. In this article, we reviewed the safety issues related to adulterated or mislabeled herbal products.

1. Introduction

In the world of globalization and online purchasing, access to various herbal preparations is easy and quick. Unintentional poisoning by herbal preparations occurs not only due to the lack of quality control during the collection and preparation of herbs but also because the long history of treatment using medicinal plants gives us a false feeling of safety and an assumption of minimal side effects (Saad et al., 2006). Only a minority of herbal preparations are registered as medicinal products that have documented quality and have been proven by studies to be effective and safe. Most herbal preparations are available on the market as food supplements and are thus subject to food legislation policies. Efficacy studies are not required (Barrueto et al., 2003; Corns, 2002), safety is assessed by different principles, and above all, quality assurance and control of food supplements are less effective.

Poor manufacturing practices can lead to the intentional or unintentional substitution of a medicinal plant due to incorrect identification, a shortage of the original plant species (Corns, 2002) or economic reasons, where a cheaper, more toxic medicinal herb replaces the more expensive one (Chan, 2003). Medicinal plants can contain different active substances (Corns, 2002) depending on the geographical location of the habitat, the time of collection, the composition of the soil, weather conditions, and any possible contaminants (Saad et al., 2006). Herbal preparations can be contaminated with heavy metals (Corns, 2002), pesticides, microorganisms and toxins (Chan, 2003), and driven by the desire for increased impact and fast action, undeclared synthetic substances, adulterants, can be illegally added to them (Barrueto et al., 2003; Corns, 2002; Klinsunthorn et al., 2011). In some products, the synthetic substance was detected during a random routine medical check or due to an unusual clinical response to treatment. In other cases, detection was due to the occurrence of adverse reactions such as agranulocytosis, Cushing's syndrome, coma, decreased blood coagulation, hypoglycemia, somnolence, massive intestinal hemorrhage, diabetes, hypertension, or arrhythmia. For example, contamination with a synthetic substance has been found in 27% of samples of Chinese medicines from the Taiwan market and 7% of the samples of Chinese medicines from the USA market (Ernst, 2002).

Traditional Chinese medicines (TCMs) are becoming increasingly popular in the Western world. Our knowledge of their pharmacology and possible toxic characteristics is still fairly limited; out of approximately 7000 plant species that are used in China for medicinal purposes, only 230 have been studied comprehensively on their pharmacology and undesirable effects (Chan, 1997). Some plants listed in the Chinese pharmacopoeia are poisonous because they contain toxic compounds. They are used in traditional Chinese medicine only with specific procedures, e.g., the processed (a special procedure is used to reduce toxicity) root of the *Aconitum* species, and the seeds of *Nuxvomica* (Chan, 2003). The toxic plants are prepared in a very specific way, which is described in the pharmacopoeia or other manuals of Chinese medicine, to reduce or remove their toxic components. In TCM herbs

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Fig. 1. The number of articles used in this review.

are often prescribed in "Fu-Fang" combinations. This means that the preparation combines processed toxic medicinal plants and non-toxic plants that are later supposed to neutralize the poison of the toxic plants (Chan, 2003).

Herbal preparations can also have interactions with prescription drugs, but only a small number of people notify their doctor or pharmacist of their use of herbal preparations because most of them are not aware of the potential dangers (Corns, 2002).

Previously we reviewed the risks arising from the use of medicinal plants with subacute and chronic toxicity (Kristanc and Kreft, 2016a, 2016b). In this article, we reviewed the risks caused by the herbal preparations, to which synthetic substances or toxic plants are intentionally (or unintentionally) added, or due to inappropriate labeling. Contamination of herbal medicinal products with metals, bacteria, mycotoxins and pesticides are also in an important safety concern, but they are not part of the scope of this review. Problem is global and articles used in our contribution come from all over the world (Fig. 1).

2. Herbal weight-loss products

People use herbal preparations for various purposes; weight loss is surely one of the most common. Some people start consuming these preparations because conventional diets have failed, while others hope that the magic slimming pill will help them lose weight without changing their lifestyle or merely buy them because herbal preparations are available freely on the internet without a prescription (Corns, 2002). An alphabetical list of adulterants found in herbal weight-loss products is presented in Table 1.

One of the most famous cases of a plant species substitution in weight-loss products is probably the series of approximately 70 cases of rapidly progressive interstitial nephritis in early nineties in Belgium. Instead of the root of *Stephania tetrandra* ("fangji" in Chinese) (Chan, 1997), the root of *Aristolochia fangchi* ("guangfangji"), which contains aristolochic acid, had been added to the weight-loss product. Aristolochic acid is a well-known nephrotoxin, its reduction forms can form covalent adducts with DNA, subsequently blocking transcription and DNA replication. (Chan, 2003; Kristanc and Kreft, 2016a; Luciano and Perazella, 2015) (Fig. 2).

In the desire for greater effectiveness and profit, illegally synthesized substances can also be added to herbal weight-loss formulations. These additives often belong to the group of anorectics, anxiolytics, antidepressants, diuretics and laxatives (Ozdemir et al., 2013). The most represented group of synthetic substances that can be found in weight-loss products are undoubtedly anorectics such as fenfluramine, sibutramine, fenproporex, diethylpropion, clobenzorex, rimonabant, phentermine, and mazindol (Carvalho et al., 2012).

One of the best-known adulterants, fenfluramine (Corns, 2002), was widely used in the 1980s and 1990s as an indirectly active sympathomimetic drug, similar to amphetamine (Brayfield, 2014). Despite being highly effective, it was determined in 1997 to cause primary pulmonary hypertension and valvular heart disease, and for this reason, it was

Table 1
Reported adulterants in alphabetical order found in herbal weight-loss products.

Reported adulerants	References
5-cyanoethyl-amphetamine	Nguyen et al., 2006
aloe-emodin	Shapira et al., 2016
Aristolochia fangchi root	Chan, 1997, Chan, 2003, Kristanc and Kreft, 2016a
caffeine	Corns, 2002, Venhuis, 2009, Ozdemir et al., 2013, Khazan et al., 2014, Hachem et al., 2016, Dastjerdi et al., 2018
clobenzorex	Parodi et al., 1993, Ku et al., 1999, Almeida et al., 2000, Carvalho et al., 2012
diazepam	Parodi et al., 1993, Almeida et al., 2000
diethylpropion	Parodi et al., 1993, Ku et al., 1999, Almeida et al., 2000, Carvalho et al., 2012
ephedra	Mlinarič et al., 1998, Corns, 2002
ephedrine	Venhuis, 2009, Khazan et al., 2014
fenfluramine	Parodi et al., 1993, Ku et al., 1999, Corns, 2002, Carvalho et al., 2012
fenproporex	Cohen, 2008, Carvalho et al., 2012
fluoxetine	Parodi et al., 1993, de Carvalho et al., 2011, 2010, Hachem et al., 2016, Dastjerdi et al., 2018
flurazepam	Parodi et al., 1993
furosemide	Moreira et al., 2013
hydrochlorothiazide	Moreira et al., 2013
lorcaserine	Hachem et al., 2014
mazindol	Carvalho et al., 2012
metformin	Parodi et al., 1993
methadone	Dastjerdi et al., 2018
N-nitroso-fenfluramine	Corns, 2002, Yuen et al., 2007
orlistat	Hachem et al., 2016
phenformin	Parodi et al., 1993
phenolphthalein	Almeida et al., 2000, Venhuis, 2009, Khazan et al., 2014, Hachem et al., 2016, Shapira et al., 2016
phentermine	Carvalho et al., 2012
phenytoin	Khazan et al., 2014
rimonabant	Carvalho et al., 2012
ritodrine	Dastjerdi et al., 2018
rizatriptan	Dastjerdi et al., 2018
sibutramine	Wang et al., 2008, Venhuis, 2009, Vaysse et al., 2010, Carvalho et al., 2012, Ozdemir et al., 2013, Khazan et al., 2014, Mathon et al., 2014, da Silva et al., 2015, Guo et al., 2015, Hachem et al., 2016, Skalicka-Woźniak et al., 2016
synephrine	Venhuis, 2009
temazepam	Ozdemir et al., 2013
thyroid hormones	Poon et al., 2008, Akinyemi et al., 2011, Dimeski et al., 2013, Khazan et al., 2014
tramadol	Dastjerdi et al., 2018
venlafaxine	Dastjerdi et al., 2018

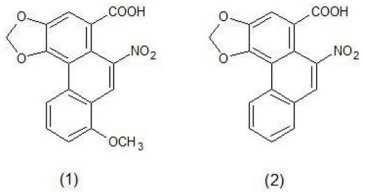

Fig. 2. Aristolochic acid is a mixture of structurally similar nitrophenanthrene carboxylic acids: 8-methoxy-6-nitro-phenanthro-(3,4-d)-1,3-dioxolo-5-carboxylic acid (1) and 6-nitro-phenanthro-(3,4-d)-1,3-dioxolo-5-carboxylic acid (2) (Luciano and Perazella, 2015).

taken off the market in the same year. Despite the ban, fenfluramine was detected in weight-loss products from China after the consumers sought medical help due to problems with hypertension, abdominal pain, nausea and palpitations. Fenfluramine was not listed in the ingredients of any of the herbal products. In some of the products, fenfluramine was found as N-nitroso-fenfluramine, which has hepatotoxic and carcinogenic properties. Because this substance can be relatively easily prepared from fenfluramine, it was probably put in the weight-

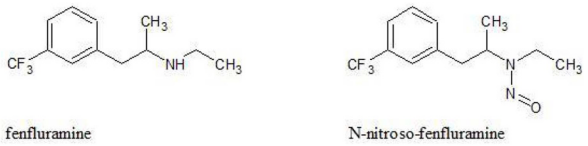

Fig. 3. Structure of fenfluramine and N-nitroso-fenfluramine.

loss products so it would not be detected by routine analyses (Corns, 2002; Ku et al., 1999; Yuen et al., 2007) (Fig. 3).

Another appetite suppressant, sibutramine, has also been taken off the market (Ozdemir et al., 2013) due to serious side effects on the cardiovascular system (Ozdemir et al., 2013), panic attacks, psychotic episodes and memory loss (Skalicka-Woźniak et al., 2016). By reducing the reuptake of serotonin and noradrenaline, and to a lesser extent dopamine (Brayfield, 2014), sibutramine reduces appetite and prolongs the feeling of satiety (da Silva et al., 2015). In a Turkish survey from 2013, sibutramine was detected in 3 out of 9 herbal weight-loss products. Sibutramine was also discovered in 16 out of 20 weight-loss products in Poland in 2007 (Ozdemir et al., 2013). Reports of sibutramine in weight-loss products have also come from Brazil (Carvalho et al., 2012), Netherland (Venhuis, 2009), Iran (Khazan et al., 2014), Switzerland (Mathon et al., 2014), China (Guo et al., 2015; Wang et al., 2008), Germany, the United Arab Emirates, Turkey, Lebanon and from France (Hachem et al., 2016; Vaysse et al., 2010), where for example they found sibutramine as a single adulterant in 43 of 164 examined weight-loss formulations and in another 23 formulations in combination with phenolphthalein. Products were mainly bought on the internet (Hachem et al., 2016). A striking example of the dangers of sibutramine is the serious psychosis that occurred in a 43-year-old female who consumed “weight-loss coffee” and stabbed herself due to that psychosis (Hachem et al., 2016; Skalicka-Woźniak et al., 2016). A case report from Israel in 2016, is also suggesting a link between a rare case of psychomotor disturbance and dietary supplement adulterated with sibutramine. A 26-year-old woman has been taking two types of dietary supplements for weight-loss, while after two weeks of consuming abnormal behavior, visual hallucinations and involuntary movements appeared. The analysis of both products revealed sibutramine and laxative phenolphtaleine in one supplement and anthraquinone laxative aloe-emodin in other. None of them was declared on the labels. While sibutramine does show a structural similarity to amphetamine, a known agent of drug-induced chorea, sibutramine was most likely the cause of it (Shapira et al., 2016).

Another representative of anorectics is fenproporex, central stimulant and indirect-acting sympathomimetic with actions similar to those of dexamfetamine. At first developed to provide appetite suppression without stimulant effects, fenproporex has since been found to have addictive potential. After oral doses, 60–80% of fenproporex is quickly metabolized to amphetamine that can be detected in urine for up to 60 h after ingestion. Among other adulterants it has been found in 4 out of 106 examined herbal weight-loss products from Brazil (Carvalho et al., 2012; Cohen, 2008) (Fig. 4).

Whereas synonym for fenproporex is *N*-2-cyanoethyl-amphetamine (Brayfield, 2014), 5-cyanoethyl-amphetamine was found in herbal weight-loss tablets “Emagrece Sim” from Brazil. After online purchasing of these diet pills, a 25-year-old woman got a persistent, increasingly severe abdominal pain that graduated into nausea and vomiting that further continued into hospital treatment (Nguyen et al., 2006).

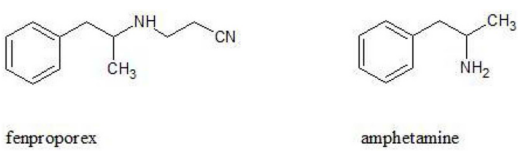

Fig. 4. Structure of fenproporex and amphetamine (Brayfield, 2014).

In samples from Brazil, another anorectic, diethylpropion (amfepramone) was proven, whereas samples of TCMs contained also another representative of anorectics, clobenzorex (Almeida et al., 2000; Ku et al., 1999). Both compounds act like central stimulants and sympathomimetics (Brayfield, 2014).

In addition to the abovementioned anorectic adulterants, the substance lorcaserine has been found in the herbal weight-loss product “Lose Quickly” in France. Lorcaserine, a selective agonist of serotonin receptors, regulates the appetite and reduces food intake. It has been shown that it can cause euphoria, hallucinations and dissociative disorder in high dosages (Hachem et al., 2014).

With purpose of hiding the undesirable effects of anorectics such as headache, nervous depression, irritability and unstable humor, benzodiazepines are often added to them. At the same time benzodiazepines can also help to reduce the anxiety that may occur in obese patients (de Carvalho et al., 2011). Temazepam, benzodiazepine that is used for the short-term treatment of insomnia was found in addition to sibutramine and caffeine in 3 out of 9 products in Poland. Its use can lead to addiction (Ozdemir et al., 2013). When they examined 20 so called “natural” capsules, used in the treatment of obesity in Brazil, anorectics and diazepam were detected in 40% (Almeida et al., 2000).

Other adulterants that can be found in weight-loss products are antidepressants. An example is fluoxetine (de Carvalho et al., 2011, 2010) that preferentially inhibit the reuptake of serotonin compared with noradrenaline, and have limited direct action at other neurotransmitter sites and therefore belongs to the group of selective serotonin reuptake inhibitors (Brayfield, 2014). In French study of 164 weight-loss formulations it was found in 4 samples. In three cases like only adulterant and in combination with orlistat in one case (Hachem et al., 2016).

Weight-loss products can also be adulterated with diuretics and laxatives that are added to give a false feeling of weight loss – the body is losing water rather than fat tissue. When herbal products for weight loss were examined in Brazil, diuretics were discovered in 8 of the 26 analyzed samples. A diuretic was even listed among the ingredients in 5 products, despite the products being advertised as “totally natural”. Without knowing the actual content, using these products can lead to dehydration and electrolyte imbalance (Moreira et al., 2013).

Laxative phenolphthalein was discovered in 20% of adulterated samples from Brazil (Almeida et al., 2000). It was also proven in samples examined in Iran, where they were analyzing formulations declared as natural herbal mixtures, mainly from China and some Southeast Asia countries (Khazan et al., 2014). In a study from Netherlands it has been found in a combination with sibutramine in several dietary supplements (Venhuis, 2009). French study confirmed phenolphthalein in 9 from 164 samples on its own and in 23 samples in a mixture with sibutramine (Hachem et al., 2016). Phenolphthalein was previously used in the treatment of constipation but has been withdrawn in many countries because of concern over its carcinogenic potential (Venhuis, 2009). It is noteworthy that the safety of that kind of combination with sibutramine had never been established in any clinical trials (Hachem et al., 2016).

The presence of other pharmaceutical substances, such as ephedrine, phenytoin, caffeine and thyroid hormones in weight-loss products has been reported in the Netherlands, UK, USA and Iran (Khazan et al., 2014).

In a big survey and health risk analysis in Netherlands where 256 weight-loss products were examined, the most frequently identified deliberately added synthetic substances were ephedrines, sibutramine, synephrine and caffeine (Venhuis, 2009). While caffeine alone is mostly safe, it can represent serious health threat in a combination with alkaloid synephrine which is also naturally present in *Citrus* species. The risk is even higher if the doses are high and different other stimulants are present (Hachem et al., 2016).

Another form of herbal weight-loss product that is widely available via the internet is a preparation that includes ephedra or a combination

Table 2
Reported adulterants in alphabetical order found in herbal sexual enhancers.

Reported adulterants	References
(R)-xanthoanthrafil	Skalicka-Woźniak et al., 2016, Bujang et al., 2017
analogues of known PDE-5 inhibitors, e.g., acetildenafil, desethylcarbodenafil, thiosildenafil	Reepmeyer et al., 2007, Balayssac et al., 2012, Vaysse et al., 2012, Jankovics et al., 2013, Gilard et al., 2015, Ulloa et al., 2015, Huang et al., 2016, Skalicka-Woźniak et al., 2016, Bujang et al., 2017, Kee et al., 2018, Wang et al., 2018
benzamidenafil	Skalicka-Woźniak et al., 2016
dehydroepiandrosterone	Gilard et al., 2015
flibanserin	Gilard et al., 2015, Skalicka-Woźniak et al., 2016
phentolamine	Balayssac et al., 2012, Gilard et al., 2015
sildenafil	Liang et al., 2006, Balayssac et al., 2012, Coralic et al., 2013, Elagouri et al., 2015, Gilard et al., 2015, Skalicka-Woźniak et al., 2016, Bujang et al., 2017, Wang et al., 2018
tadalafil	Gilard et al., 2015, Skalicka-Woźniak et al., 2016, Bujang et al., 2017, Wang et al., 2018
testosterone	Gilard et al., 2015
tetrahydropalmatine	Balayssac et al., 2012
vardenafil	Gilard et al., 2015, Skalicka-Woźniak et al., 2016
yohimbine	Gilard et al., 2015

of ephedra and caffeine (sometimes in the form of guarana extract). Ephedra, “Ma Huang” in Chinese (Corns, 2002), contains ephedrine and pseudoephedrine with sympathomimetic action, acting agonistically on the alpha and beta adrenergic receptors (Brayfield, 2014). Before the prohibition, ephedra was added to herbal preparations, including athletic performance stimulators, without being properly declared on the packaging (Mlinarič et al., 1998). In some of the described examples, serious side effects to the central nervous system and dangerous cardiovascular events occurred. The Food and drug administration (FDA) has completely banned preparations containing ephedra in the USA; in Europe, only food supplements are prohibited. Despite this, unregistered preparations are widely available via the internet (Corns, 2002).

In an Italian survey from 1993 metformin, flurazepam and phenformin were already proven in preparations with slimming activity besides above mentioned clobenzorex, diazepam, diethylpropion, fenfluramine and fluoxetine (Parodi et al., 1993).

Triiodothyronine (T3) was also detected in dietary supplements in USA. A case report of two patients that developed thyrotoxic hypokalemic periodic paralysis 2–3 weeks after consuming weight-loss formulation is described. Condition is an endocrine emergency and can cause arrhythmia and death (Akinyemi et al., 2011). While in above mention example only T3 has been fund, there are reports of formulations containing thyroid tissue, mainly porcine, which contain thyroid extract and usually both T4 (thyroxine) and T3 hormones. Typical symptoms of hyperthyroidism and related cardiovascular complications can occur at consuming that kind of adulterated formulations (Dimeski et al., 2013). In April 2006, French health authorities published a report of one death and several hospital admissions after taking a “slimming aid” made of powdered thyroid extract (Poon et al., 2008).

Examination of 164 weight-loss formulations from France interestingly showed the presence of sildenafil in 12 samples. It was found alone, in combination with phenolphthalein, sibutramine or with both. It had been found in such low dosages by comparison to the therapeutic doses that it was concluded that the presence of sildenafil is pretty likely due to cross contamination during the process of manufacturing. In another case of “X-treem slimming” formulation they discovered differences inside the box - adulterants among individual blisters were different. Research also revealed changes in composition within the same branded products and therefore different adulterants among batches (Hachem et al., 2016).

The same phenomenon was also observed in recently published study from Iran, where they were examining 61 herbal weight-loss supplements. The analysis of the same brand from different herb shops, revealed totally different chromatographic profiles. Compositions of the formulations were not stated on the labels or in a package leaflets. 72% of samples were adulterated with at least one synthetic substance, most commonly with tramadol and caffeine. Other adulterants were antidepressants fluoxetine and venlafaxine, antimigraine drug rizatriptan, opioid analgesic methadone and a direct-acting sympathomimetic with mainly beta-adrenergic activity and a selective action on beta-2-receptors ritodrine (Brayfield, 2014; Dastjerdi et al., 2018).

3. Herbal sexual enhancers

FDA research in the USA between 2007 and 2014 showed that undeclared synthetic substances were most notably present in herbal sexual enhancers - preparations used to increase libido (sexual desire) and reduce erectile dysfunction (Skalicka-Woźniak et al., 2016). An alphabetical list of adulterants found in herbal sexual enhancers is presented in Table 2.

Phosphodiesterase type 5 (PDE-5) inhibitors are a group of substances used for the treatment of erectile dysfunction. In the past few years, it has been found that they were in many cases added to herbal preparations that were advertised as “100% natural aphrodisiac”. It is obvious that the unaware usage of such preparations is dangerous, as they are associated with adverse reactions such as headache, blushing, dyspepsia, visual disturbances, muscle pains, loss of vision and blindness. PDE-5 inhibitors may also cause potentially serious drug-drug interactions. Patients who use these preparations in combination with nitrates as part of their treatment can develop life-threatening hypotension (Brayfield, 2014; Shi et al., 2014) (Fig. 5).

Sildenafil, vardenafil and tadalafil are the main PDE-5 inhibitors found in herbal preparations. However, their analogues, which cannot be so easily defined in routine screening due to small structural changes in the molecular structure, can also appear. These analogues present an even greater risk due to their unknown safety, as the adverse reactions are unpredictable. Acetildenafil, an analogue of sildenafil, is not selective and causes visual disturbances even at minimum dosages due to inhibition of phosphodiesterase type 6 (Skalicka-Woźniak et al., 2016). The majority of analogues have been reported from the Asian countries (67%), followed by Europe (22%) and North America (11%) (Kee et al., 2018).

Up to now, 80 illicit analogues of PDE-5 inhibitors have been discovered, and unfortunately, that number is rising (Huang et al., 2016; Jankovics et al., 2013; Kee et al., 2018; Reepmeyer et al., 2007; Skalicka-Woźniak et al., 2016; Ulloa et al., 2015; Vaysse et al., 2012). Most often represented are sildenafil analogues with a share of 62% (Kee et al., 2018). One example is the discovery of a new sildenafil analogue desethylcarbodenafil in a maca-containing herbal supplement, claimed to remedy erectile dysfunction, in Taiwan (Huang et al., 2016).

In a French study from 2012, 8 out of the 9 reviewed samples of herbal dietary supplements for sexual performance enhancement

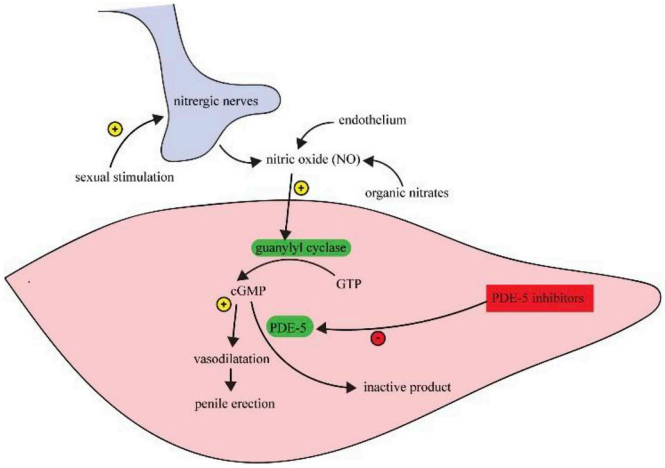

Fig. 5. Mechanism of action for PDE-5 inhibitors and the interaction of PDE-5 inhibitors with organic nitrates. Sexual stimulation releases nitric oxide (NO) from nitrergic nerves and activates guanylyl cyclase in vascular smooth muscle cell in the corpora cavernosa. That causes increase in cGMP production and therefore vasodilatation and penile erection. cGMP is inactivated by PDE-5, so PDE-5 inhibitors potentiate NO and promote penile erection. NO from organic nitrates (e.g. glyceryl trinitrate) is also potentiated. That leads to generalized vasodilatation and hypotension. Schematic presentation adapted from: (Rang & Dale's, 2016.

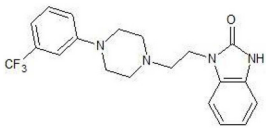

Fig. 6. Chemical structure of flibanserin.

intended for the South European market contained illicitly added synthetic substances. Four preparations contained propoxyphenyl-thiohydroxyhomosildenafil, a non-approved sildenafil analogue; one contained thiosildenafil; two contained sildenafil in combination with tetrahydropalmatine, which has no proven effects on erectile dysfunction; and one contained phentolamine, which is also a drug that is not approved for increasing male sexual performance (Balayssac et al., 2012).

Two years later, also in France, 150 herbal preparations that were marketed as 100% natural preparations for improving sexual performance were reviewed. Of these, 61% contained PDE-5 inhibitors, and in 5.5%, other substances were discovered, such as yohimbine, flibanserin, phentolamine, dehydroepiandrosterone and testosterone (Gilard et al., 2015).

In some cases, PDE-5 inhibitors, which are not analogues of currently known substances, e.g., benzamidenafil and (R)-xanthoanthrafil, have been found. Adulterants can also be present in herbal preparations to increase women's libido. Flibanserin, a substance that affects the serotonin system, was discovered in them (Skalicka-Woźniak et al., 2016) (Fig. 6).

Even though illegal chemical substances have been frequently detected in dietary supplements or in TCMs in past years, recent study where they bought samples of traditional Chinese patent medicines (TCPMs) and dietary supplements in local drug shops or markets in China, showed that among 32 batches of investigated samples of TCPMs, none of them was adulterated. However, 28 of 40 batches of dietary supplements were positive. They revealed illicitly added sildenafil, tadalafil, aildenafil and sulfoaildenafil (Wang et al., 2018).

Malaysia market survey between April 2014 and April 2016 where they examined 62 products that claimed to enhance man's sexual health revealed that of 62 herbal formulations, 82% were adulterated with at least one PDE-5 inhibitor or analogue. The striking fact is that one of the samples contained even five different PDE-5 inhibitors (Bujang et al., 2017).

Report of adulterated herbal sexual enhancers is also coming from Egypt (Elagouri et al., 2015) and from the USA, where usage of herbal preparation Africa Black Ant, marketed for erectile dysfunction, in which sildenafil was found, ended with 5 days of priapism for a 49-year-old-man. He also consumed an unknown amount of illicit methamphetamine and had been on antiretroviral therapy (Coralic et al., 2013).

4. Herbal preparations for treatment of rheumatic and inflammatory diseases

Rheumatic disease is another condition in which people often use herbal preparations. Their adulteration with synthetic substances is frequently accompanied by adverse reactions, including gastrointestinal hemorrhages. An alphabetical list of adulterants found in herbal preparations for treatment of rheumatic and inflammatory diseases is presented in Table 3.

In Germany, a female rheumatic patient bought a Vietnamese powdered herbal preparation, advertised as an antirheumatic medicine. This herbal preparation was later revealed to contain acetaminophen, indomethacin, sulfamethoxazole and trimethoprim in addition to the herbal ingredients (Wiest et al., 2014).

Similarly an Indonesian herbal formulation in a sachet, claimed to treat conditions such as rheumatism, body ache and bone ache, muscle and joint pain, giddiness, toothache, backache and chronic numbness,

Table 3
Reported adulterants in alphabetical order found in herbal preparations for treatment of rheumatic and inflammatory diseases.

Reported adulterants	References
acetaminophen	Wiest et al., 2014, Chong et al., 2015
antibiotics e.g., sulfamethoxazole	Wiest et al., 2014, Chong et al., 2015
antifungals, e.g., clotrimazole, ketoconazole	Skvarc, 2014, Chong et al., 2015
benzodiazepines	Chong et al., 2015
beta-2-receptor agonists	Chong et al., 2015
betamethasone	Chong et al., 2015
betamethasone dipropionate	Skvarc, 2014
betamethasone valerate	Skvarc, 2014
clobetasol	Chong et al., 2015
clobetasol propionate	Skvarc, 2014
clobetasone butyrate	Skvarc, 2014
cortisone acetate	Zhou et al., 2016
dexamethasone	Segasoty and Samad, 1991, Skvarc, 2014, Chong et al., 2015, Park et al., 2016
dipyrone	Bogusz et al., 2006
diuretics	Chong et al., 2015
fluocinonide	Chong et al., 2015
H-1-receptor antagonists	Chong et al., 2015
H-2-receptor antagonists	Chong et al., 2015
hydrocortisone	Skvarc, 2014
hydrocortisone acetate	Zhou et al., 2016
methylxanthines e.g., caffeine	Lau et al., 2003, Chong et al., 2015
non-steroidal anti-inflammatory drugs, e.g.,ibuprofen, indomethacin, nimesulide, oxyphenbutazone, phenylbutazone	Segasoty and Samad, 1991, Lau et al., 2003, Bogusz et al., 2006, Liang et al., 2006, Swedish Medical Products Agency, 2009, Wiest et al., 2014, Chong et al., 2015
opioids	Chong et al., 2015
oral antidiabetic drugs	Chong et al., 2015
PDE-5 inhibitors	Chong et al., 2015
prednisolone	Chong et al., 2015
prednisone	Chong et al., 2015, Zhou et al., 2016
prednisone acetate	Chong et al., 2015, Zhou et al., 2016
triamcinolone	Chong et al., 2015
trimethoprim	Wiest et al., 2014
Wintergreen essential oil	Baxter et al., 2003

revealed its true content after analysis. Product was adulterated with nonsteroidal anti-inflammatory drug phenylbutazone, stimulant caffeine and with a trace of oxyphenbutazone (Lau et al., 2003). Another examined herbal powder from Indonesia was adulterated with phenylbutazone and dipyrone (Bogusz et al., 2006).

Glucocorticoids prednisolone, betamethasone, dexamethasone, prednisone, cortisone acetate, clobetasol, fluocinonide, triamcinolone and hydrocortisone acetate are also on the list of illegal additives to TCMs used for the treatment of rheumatic diseases. With their effect in treatment of pain, inflammation and rheumatism, potentially serious side reactions like immunosuppression, increased skin fragility, osteoporosis, peptic ulcer disease, etc. and even potentially fatal complications can occur. The risk of these undesirable effects is of course growing with prolonged time of use and with use of high doses without medicinal supervision (Chong et al., 2015; Park et al., 2016; Zhou et al., 2016). In analysis of 42 batches of herbal medicines in China, 52% of the samples were positive for presence of glucocorticoids (Zhou et al., 2016).

In samples of proprietary Chinese medicines with proven corticosteroids in it co-adulterants were also detected. The most common were non-steroidal anti-inflammatory drugs, mostly in formulations indicated against pain, and histamine H-1-receptor antagonists in formulations for dermatological use. Acetaminophen, H-2-receptor antagonists, diuretics, benzodiazepines, methylxanthines, antifungals, antibiotics, beta-2-receptor agonists, oral antidiabetic drugs, PDE-5 inhibitors and even opioids were also detected (Chong et al., 2015).

Case report from Malaysia presents us with a 73-year-old woman with osteoarthritis of both knees, which has been consuming an herbal preparation daily for the past 10 years. Renal papillary necrosis had been documented and gastroscopy revealed gastric ulcer. Analyses of herbal product revealed phenylbutazone and traces of dexamethasone (Segasoty and Samad, 1991).

Another example is a 67-year-old-man with a history of psoriasis, diabetes, hypertension and chronic renal impairment. After 2-months usage of proprietary Chinese medicine preparation for psoriasis, after which his skin condition dramatically improved, he presented in hospital with acute renal failure and respiratory distress. Prednisone acetate was found in the preparation (Chong et al., 2015).

An analysis of 212 herbal preparations for the treatment of rheumatic diseases in South Korea showed the presence of synthetic substances in only 2%; however, this will likely rise due to the demand for greater efficacy (Park et al., 2016).

In Sweden and Norway, the herbal food supplement Fortodol has been available for the treatment of arthritis, muscular pains and headaches since 2004. The Swedish and Norwegian medicine agencies issued a warning in 2009 and published nine known examples of liver damage, two of which ended in death. A detailed analysis of the product in two of the nine samples revealed the presence of a non-steroidal, anti-inflammatory substance called nimesulide, which can cause serious liver damage (Swedish Medical Products Agency, 2009).

Another case is described in the literature where a demented man ingested a massage oil intended for muscular pain, labeled only in Chinese. It turned out that its main ingredient was the essential oil “Wintergreen”. The oil is obtained from the species *Gaultheria* and contains 98–100% methyl salicylate, which is quickly absorbed if ingested and causes symptoms of salicylate poisoning (Baxter et al., 2003).

Illicit synthetic substances in natural skin care products are in most caseslocal corticosteroids that are used to treat inflammatory skin diseases, mainly psoriasis and eczema. In creams, the corticosteroids betamethasone dipropionate, clobetasol propionate, hydrocortisone, betamethasone valerate, clobetasone butyrate and dexamethasone, as well as the antimycotics clotrimazole and ketoconazole, have been found (Skvarc, 2014). In research at the Faculty of Pharmacy in Ljubljana, a corticosteroid, betamethasone dipropionate, was found in an ointment, called “Melem by Dr. Vasić”, which is advertised as a treatment for eczema, psoriasis, lichen planus, neurodermatitis, rosacea and atopic dermatitis. Due to its declared natural ingredients (medicinal plants and bee products are listed among the ingredients), the ointment is extremely popular with parents who do not want to use corticosteroid creams on their children (Skvarc, 2014).

Table 4
Reported adulterants in alphabetical order found in herbal preparations for blood sugar regulation.

Reported adulterants	References
chlorpropamide	Li et al., 2010
glibenclamide	Ku et al., 2003, Bogusz et al., 2006, Li et al., 2010, Guo et al., 2014, Vaclavik et al., 2014, Steyn et al., 2018
gliclazide	Li et al., 2010
glimepiride	Li et al., 2010
metformin	Li et al., 2010, Guo et al., 2014, Vaclavik et al., 2014, Steyn et al., 2018
mitiglinide	Li et al., 2010
nateglinide	Li et al., 2010
phenformin	Li et al., 2010, Guo et al., 2014
rosiglitazone	Li et al., 2010, Vaclavik et al., 2014

5. Herbal preparations for blood sugar regulation

The usage of added illicit synthetic substances has also been reported in herbal preparations used for blood sugar regulation (Table 4). The most frequently found illicit substances are glibenclamide, rosiglitazone and metformin (Vaclavik et al., 2014) (Fig. 7).

Undesirable effects such as hypoglycemia, gastrointestinal reactions and liver or kidney damage can occur at patients taking a large amount of these adulterants (Guo et al., 2014).

A case report from UK describes a case of 58-year-old woman with a history of diabetes type 2, that replaced some of her antidiabetic drugs with herbal remedy purchased in India. Manufacturer claimed it was a cure for diabetes, rather than a treatment. However, after recurrent hypoglycemia and gradual decline in her renal function, it turned out that “miracle tablets” contained glibenclamide and metformin (Steyn et al., 2018).

Survey from China revealed antidiabetic drugs in 7 out of 34 examined dietary supplements, while all 63 batches of herbal medicines were negative. Metformin, phenformin and glibenclamide were detected (Guo et al., 2014).

Glibenclamide was also proven in a sample of TCMs in Taiwan (Ku et al., 2003) and as most common adulterant in a survey of proprietary Chinese medicines and dietary supplements for diabetes treatment from 2010. Other detected adulterants were metformin, rosiglitazone, glimepiride, phenformin, gliclazide, chlorpropamide, nateglinide and mitiglinide (Li et al., 2010).

Unlabeled herbal tablets “against diabetes” from Lebanon where recommended daily dose was 15 tablets revealed their actual content of 7.5 mg glibenclamide per tablet after analysis. Glibenclamide was also

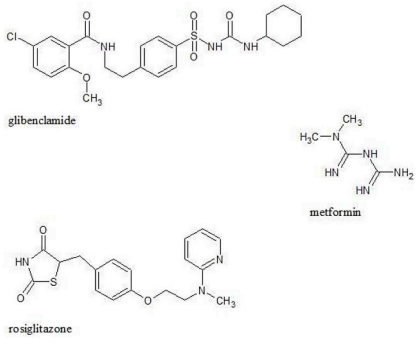

Fig. 7. Chemical structures of glibenclamide, rosiglitazone and metformin.

Table 5
Reported adulterants in alphabetical order found in herbal preparations for blood pressure regulation.

reported adulterants	references
amlodipine	Kesting et al., 2010, Vaclavik et al., 2014, Khan et al., 2016
captopril	Liang et al., 2006
clonidine	Vaclavik et al., 2014
hydrochlorothiazide	Vaclavik et al., 2014, Khan et al., 2016
indapamide	Kesting et al., 2010, Vaclavik et al., 2014
nifedipine	Liang et al., 2006, Khan et al., 2016
Rauwolfia species	Gallo et al., 2012
valsartan	Kesting et al., 2010, Vaclavik et al., 2014
verapamil	Khan et al., 2016

discovered in an amount of 4.5 mg per gram in an herbal powder from Jordan. These products were labeled with the instructions of use that would be leading to severe hypoglycemia (Bogusz et al., 2006).

6. Herbal preparations for blood pressure regulation

Illegal synthetic substances such as amlodipine, indapamide, valsartan, clonidine and hydrochlorothiazide have also been detected in herbal preparations for blood pressure regulation (Vaclavik et al., 2014). An alphabetical list of adulterants found in herbal preparations for blood pressure regulation is presented in Table 5.

Pakistani survey from 2016 which examined local herbal antihypertensive formulations, revealed various contents of calcium channel antagonists amlodipine, verapamil and nifedipine and a diuretic hydrochlorothiazide in combination with amlodipine (Khan et al., 2016). Survey from Denmark, where they examined “Gold Nine Soft Capsules”, herbal Chinese formulation for treatment of hypertension, revealed hidden amlodipine, indapamide and valsartan (Kesting et al., 2010).

Unexpected effectiveness of dietary supplement “Olivis”, marketed in Italy as an adjunct to hypertension therapy, raised concerns about its content. Addition of an extract from *Rauwolfia* species was suspected when alkaloids reserpine and ajmaline were found in a sample (Gallo et al., 2012).

7. Herbal preparations for treatment of central nervous system (CNS) disorders

An alphabetical list of adulterants found in herbal preparations for treatment of CNS disorders is presented in Table 6.

A Swedish report specifies nine instances of death in a one-year period due to the ingestion of the powdered leaves of *Mitragyna speciosa*, also known as “Kratom”, to which the active metabolite of tramadol, O-desmethyltramadol, was added. The tropical tree *Mitragyna speciosa* thrives in Southeast Asia as well as in parts of Africa and is used in traditional medicine for several indications: at low dosages, it acts as a stimulant; however, in high dosages, sedation and similar behavior to that following the use of opioids can occur. In recent years, kratom has gained its popularity as a recreational drug. The main substance, which is also the cause of the opioid reaction to μ-receptors, is mitragynine. In combination with another μ-agonist, O-desmethyltramadol, it constitutes enormous potential for misuse and overdose, which can end in death (Kronstrand et al., 2011; Warner et al., 2016).

In the literature, a case of a 33-year-old female from Hong Kong with an 8-year history of epilepsy is described. She was being treated with sodium valproate and carbamazepin. She bought a natural preparation declared to contain only natural Chinese medicinal ingredients effective in epilepsy control. It was later revealed that the capsules contained phenytoin, carbamazepine and valproate (Lau et al., 2000). A Chinese medicine “wuyoufun-13” was found to contain *Coptidis rhizoma*, a medicinal plant with antibacterial and anticonvulsant activity, but this plant was not labeled on the product (Chen et al., 2000).

Besides adulteration with synthetic substances, the deliberate or accidental addition of other plant species also occurs. 40% of the tested samples of products labeled to contain St. John's wort (*Hypericum perforatum*) dry extracts or herb, failed identification test made with flavonoid fingerprints. In addition adulteration with dyes was also found (Frommenwiler et al., 2016).

Examination of 11 *Ginkgo biloba* food supplements on the European market revealed 4 cases where extracts from other undeclared plants were present, 2 cases where the content was much lower than declared and 1 case where the product contained powdered leaf of *Gingko biloba* instead of extract as declared (Czigle et al., 2018).

8. Herbal preparations with multiple indications

An alphabetical list of adulterants found in herbal preparations with multiple indications is presented in Table 7.

An example from the USA describes a woman who, 8 h after the ingestion of an herbal preparation for body detoxification made of “plants from the Amazon rainforest”, experienced nausea, vomiting and overall weakness. Her blood pressure in the hospital was 86/30 mmHg, and her heart rate was 30 beats a minute. Laboratory analyses showed the presence of digoxin and the active metabolite digitoxin, cardioactive steroid glycosides that causes serious poisoning (Barrueto et al., 2003).

Wide range of adulterants was proven in survey from China in 2005, when they examined over 200 samples of herbal medicines and dietary supplements. 74 results were positive. Most commonly they found sildenafil, famotidine, ibuprofen, promethazine, diazepam, nifedipine, captopril, amoxicillin and dextromethorphan. For example, from 47 examined formulations, claimed to be capable of “keeping fitness of stomach”, 18 were adulterated with famotidine (Liang et al., 2006).

A Hong Kong report states that most of the poisonings are due to herbs that contain alkaloids from plants of the *Aconitum* species and plants that contain tropane alkaloids. An increased number of poisonings with tropane alkaloids between 2000 and 2012 has been mainly associated with the presence of plants containing tropane alkaloids, e.g., substituting the non-toxic flowers of *Campsis grandiflora* with the toxic flowers of *Datura metel*. Both flowers look very similar in their dry state (Chan, 2016a).

Table 6
Reported adulterants in alphabetical order found in herbal preparations for treatment of CNS disorders.

Reported adulterants	References
O-desmethyltramadol	Kronstrand et al., 2011, Warner et al., 2016
carbamazepine	Lau et al., 2000
Coptidis rhizoma	Chen et al., 2000
dyes in products labeled to contain St. John's wort	Frommenwiler et al., 2016
extracts from undeclared plants in *Ginko biloba* food supplements	Czigle et al., 2018
other plant species in products labeled to contain St. John's wort	Frommenwiler et al., 2016
phenytoin	Lau et al., 2000
valproate	Lau et al., 2000

Table 7
Reported adulterants in alphabetical order found in herbal preparations with multiple indications.

Reported adulterants	References
Aconitum species	Ono et al., 2009, Singhuber et al., 2009, Chan 2010, Chan, 2011, Chen et al., 2015, Chan, 2016b
amoxicillin	Liang et al., 2006
Datura metel flowers	Chan, 2016a
dextromethorphan	Liang et al., 2006
diazepam	Liang et al., 2006
digoxin	Barrueto et al., 2003
famotidine	Liang et al., 2006
promethazine	Liang et al., 2006

Throughout history, people in the territories of China and Japan have widely used the root or tuber of the *Aconitum* species to treat colds, polyarthralgia, wounds, depression, diarrhea and heart failure. The *Aconitum* species (more than 300 over the world, with only two listed in the Chinese pharmacopoeia (Singhuber et al., 2009)) contain aconitine, mesaconitine, hypaconitine and other alkaloids, known to be cardiotoxic and neurotoxic, in their roots and root tubers. Precisely because of its further use in TCM, aconite poisoning is still frequent (Chan, 2011). Even though reports are infrequent in Europe, the *Aconitum* species have also been used there for centuries. Due to their toxicity, they have not been used in official medicine for many years, although they are still used in folk medicine in certain places in Slovenia (Povšnar et al., 2017). In TCM, products from the *Aconitum* species are used only after processing, which reduces the toxic alkaloid content, and only in the form of a decoction. The user should be carefully instructed on the preparation and the maximum permissible amount for preparing a decoction, otherwise poisoning can occur. As they contain highly toxic alkaloids, the roots of *Aconitum* species must be boiled for a specific amount of time before ingestion; this is how the toxic alkaloids hydrolyze to less toxic compounds (Ono et al., 2009). Cases of poisoning and the occurrence of paralysis, palpitations, vomiting, diarrhea and nausea following non-compliance with the method of preparation are described in the literature (Chan, 2016b). In cases where root of the *Aconitum* species is not listed among the ingredients (Chan, 2010) the amount of the root in the preparation can't be foreseen, and the product is not prepared as required for this species. Such "hidden roots" of the *Aconitum* species pose a great danger (Chan, 2016b). More serious poisoning can also lead to hypotension, sinus tachycardia, ventricular ectopic beats, ventricular arrhythmia and asystole (Chan, 2011). Death usually occurs due to refractory ventricular arrhythmia and cardiac arrest (Chen et al., 2015).

9. Conclusion

Compared to synthetic substances whose adverse reactions have been widely researched and published, most people are unaware of the risks of herbal preparations due to the common conviction of the safety of medical plants. It must be stressed that herbal preparations do not generally reduce symptoms immediately, so if immediate relief occurs, we must consider the possible presence of synthetic substances.

This intentional addition of synthetic substances, unintentional and intentional addition of other plant species or mislabeling can cause various adverse reactions or even death. Although there is no overall statistics to show the extent of it, reports are coming from all over the world.

Nevertheless, it must be noted that herbal preparations, when used correctly, are, in most cases, relatively harmless and can be useful.

One such example is ephedra, which is used in traditional medicine in small doses for coughs and runny nose, rather than as a stimulant or weight-loss supplement. Such usage in higher doses and for an extended period of time caused serious adverse reactions, which have been described in the literature.

With this contribution we wanted to alert people to be careful when choosing and buying herbal preparations.

We stated some reference points that can be of use in the critical analysis of an individual herbal preparation. In most parts of the world (including the Western world), there are no efficient official institutions for the control of herbal food supplements, so we must rely on our own judgment and the manufacturer's honesty.

Conflicts of interest

None.

Transparency document

Transparency document related to this article can be found online at https://doi.org/10.1016/j.fct.2018.10.043.

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