Contamination of Sports Supplements with Novel Psychoactive Substances: An Old History with New Players

Irene E. Mazzoni

Historic Background: Traditional Medicines and Natural Products

Since ancient times, humans have relied on nature for their basic needs including medicines. Plants are considered a rich source of bioactive chemicals and have been the basis of traditional medicine systems for thousands of years [1]. In addition, many active compounds have been identified and isolated from these plants and are part of modern conventional therapeutic medications [2]. Fossil records date human use of medicinal plants from 60,000 years ago. Among the ancient civilizations, India is known to be the richest repository of medicinal plants. Ancient China developed systemic pharmacopeias as early as 3000 BC. Aboriginal people from America, Africa and Oceania have been using natural products as medicines for centuries [3–7]. Drugs acting on the nervous system, including psychoactive substances (PS), are present in many plants. One of the first used analeptic stimulants was strychnine, an alkaloid obtained from *Strychnos nux-vomica.* The poisonous and medicinal effects of strychnine have been well known since ancient times in China and India and more recently was also used worldwide in medicinal tonics until the early twentieth century, when it was abandoned due to its toxicity [8, 9]. Other analeptics found in plants include bicuculline, present mainly in *Dicentra cucullaria* [8, 10], and picrotoxin, obtained from the shrub *Anamirta cocculus* [2, 7]. In addition, xanthines like caffeine, theophylline and theobromine, naturally occurring in coffee and tea, are also considered mild analeptics [8, 11]. Cardiostimulants like scillaren A can be found in *Urginea (Scilla) maritima* and was known by the ancient Romans and Syrians, who used it for the treatment of oedematous states [12]. Plants of the

I. E. Mazzoni (✉)
Science and Medicine Department, World Anti-Doping Agency (WADA), Montreal, QC, Canada
e-mail: Irene.Mazzoni@wada-ama.org

O. Rabin, O. Corazza (eds.), *Emerging Drugs in Sport*,
https://doi.org/10.1007/978-3-030-79293-0_2

Digitalis family are rich sources of cardiotonics such as digitalin, digoxin, digitoxin, deslanoside and lanatosides and have been used for heart conditions since the thirteenth century [2, 14]. The stimulant properties of coca leaves, the source of cocaine, were known to indigenous people of the Andes since prehistory [13]. Coca was widely used to combat cold, fatigue, pain and hunger as well as in religious ceremonies. During the Inca Empire, coca was reserved for the elite classes, but after the Spanish conquest, it was made available to all the population, as it enabled peasants to work longer and harder and suppressed their appetite [14]. *Papaver somniferum* has been cultivated for several thousands of years in Mesopotamia for its poppy seeds, used for baking, and for the milky latex, opium. The dried latex contains numerous alkaloids including morphine, codeine, thebaine, noscapine, narceine and papaverine, which account for most of opium's narcotic and medicinal properties such as analgesia, antitussive and antidiarrheal effects [15]. Finally, several plants containing PS with hallucinogenic properties have been used in religious rituals throughout history. Known as entheogens, they include the peyote cactus, widely used in the Aztec Empire which contains mescaline as PS [16]; the ayahuasca drink prepared by Amazonian natives since pre-Columbian times, which contains MAO and serotonin inhibitors [17]; "magic mushrooms" containing psilocybin, used for centuries by Mexican aboriginal people [18]; and the iboga plant containing ibogaine, utilized by tribes of West Africa, at low doses as a stimulant to prevent fatigue and dull hunger and thirst and at high doses as hallucinogens during religious rituals [19].

Classical Doping Psychoactive Substances in Supplements

PS have long been used to enhance physical and mental performance. For example, Inca messengers used coca to help them run long distances at high altitudes [20]. Stimulants have also been extensively used in warfare to enhance stamina and alertness and to cope with traumas of the battlefield. A mixture of herbs containing stimulants, painkillers and hallucinogens was reported to be used by the Zulu tribes during their stand against British troops in 1879 [21]. While cocaine was the drug of choice during World War I, amphetamine and methamphetamine were used extensively during World War II [21–23]. Carphedon (phenylpiracetam) was developed in 1983 as a medication for Soviet cosmonauts to increase physical, mental and cognitive activities in space [24]. Amphetamines are also used by the working class to extend their working hours or facilitate hard labour [25], while prescription drugs like methylphenidate or dexamphetamine are often used by students in an attempt to enhance their learning skills [26]. The pharmacologic properties of many PS make them very attractive and valuable doping substances in sport. Some even claim that the word doping is originally derived from the use by some African tribes of a stimulant liquor called "dop" [27]. Precursors of modern-day supplements containing PS include the mixture of brandy and the stimulant strychnine that almost kills Thomas Hicks, the winner of the 1904 Olympic marathon in St Louis [28].

Strychnine and mixtures of heroin, cocaine and caffeine were commonly used by high-level athletes until the 1920s [29]. The use of stimulants in-competition was first banned by the International Association of Athletics Federations (IAAF) in 1928. However, this did not deter their use which continued to increase, in parallel with a more liberal view of society on drugs. The phenethylamine derivative amphetamine has played a prominent role in doping. The Dane Kurt Jensen was the first recorded death at the modern Olympics, collapsing from an amphetamine overdose at the 1960 Rome games, while the British cyclist Tommy Simpson died during the 1967 Tour de France after consuming amphetamines and brandy to combat the effects fatigue [30]. As a response to the growing doping problem, the International Olympic Committee (IOC) issued the first list of prohibited substances for the 1968 Olympic Games. This list included PS encompassed under the categories "Sympathomimetic Amines (e.g., amphetamine), ephedrine and similar substances", "Stimulants of the central nervous system (strychnine) and analeptics" and "Narcotics and analgesics (e.g., morphine), similar substances" [31]. The World Anti-Doping Agency (WADA), who in 2001 took over the regulation of the use of substances and methods in sports, continued with the ban of PS under three different categories: stimulants, narcotics and cannabinoids [32, 33]. Nevertheless, amphetamine and cocaine are still at the top of positive doping control tests in the class of stimulants [34]. Ephedrine alkaloids also belong to the group of traditional PS found in supplements. The ephedra plant (Ma Huang), which apart from ephedrine also contains pseudoephedrine and minor components, has been used in China for medicinal purposes for thousands of years [35]. Ephedrine became the standard medication for treatment of asthma in the first half of the twentieth century until the arrival of more efficacious medicines like beta-2-agonists and glucocorticoids [36, 37]. Its decline in use as a prescribed medicine in the 1960s was followed by an increase as a prominent component of nutritional supplements marketed as "natural stimulants", targeting weight loss and sports performance enhancement [35, 37–40]. A number of deaths and hundreds of adverse reactions associated with the use of ephedra-containing supplements in the USA prompted their complete ban in 2004 [41–47]. Fatal cases included those of professional athletes such as Korey Stringer in 2001 and Steve Bechler in 2003 [48]. Nevertheless, ephedra supplements are still widely available on the Internet. Other appetite suppressants such as fenfluramine, phentermine, phenmetrazine, fencamfamine, mephentermine and benfluorex are also commonly found as supplements claiming anorexigenic effects [49]. One of the minor alkaloids present in Ma Huang plant is cathine (norpseudoephedrine), and as expected, it is also found in dietary supplements containing this plant and its extracts [35, 38, 45]. However, the main natural source of cathine is the evergreen shrub *Catha edulis* (khat), grown mostly in East Africa, Yemen and other Middle Eastern countries. Khat contains, in addition to cathine, other amphetamine-like alkaloids such as cathinine and norephedrine [50]. Khat is traditionally used for its stimulant properties, sought to increase work capacity, improve sports and mental performance and improve alertness [50]. Although consumption of khat is mainly restricted to the native growing areas, cathine and cathinone are also found as part of manufactured dietary supplements, not only as natural component of the

ephedra-derived supplements as noted before but as adulterants or main component of the supplement as well [40, 51]. A number of discontinued medications with psychoactive properties are also part of the arsenal used in supplements targeting athletes. As examples, we find methylhexaneamine (also known as, e.g., methylhexamine, 1,3-dimethylamylamine, 1,3-DMAA, dimethylamylamine), an indirect sympathomimetic marketed as an inhaled nasal decongestant from 1948 until the 1970s under the trade name Forthane [52]. It reappeared in dietary supplements in 2006 under the trademarked name Geranamine. In order to disguise its synthetic origin, the supplements listed "geranium oil" or "geranium extract" as source. However, currently there is no evidence that methylhexanamine is present naturally in plants [53–56]. Similarly, methylsynephrine is claimed to be a component of bitter orange (*C. aurantium*), but efforts to identify it as naturally present in plants have failed [57–59]. In fact, methylsynephrine is the approved drug oxilofrine which is used to treat hypotension in a handful of countries [60]. Finally, the stimulant and appetite suppressant sibutramine was withdrawn from the market in many countries due to the risk of cardiovascular adverse events. Nevertheless, sibutramine and derivatives such as desmethylsibutramine and didesmethylsibutramine are found as components of many diet pills and anorexigenic supplements [49, 61–63]. This is another example of how the dietary supplement industry surreptitiously reintroduces discontinued medications into their products.

Novel Psychoactive Substances (NPS) in Dietary Supplements and Doping

NPS in the Prohibited List

Novel psychoactive substances (NPS) are unregulated substances with no legitimate medical use and are made to copy the effects of controlled substances and evade detection [64]. They are introduced in and withdrawn from the market in quick succession to escape or hamper law enforcement efforts to contain their manufacture and sale. Despite being advertised as "legal highs" with the pretention that they are safer than commonly used drugs of abuse, these synthetic designer versions are in many cases stronger than the natural product. As the dietary supplement market rapidly expands, the probability of introducing NPS into these products increases. The athletic population is commonly targeted for products marketed to enhance performance, power, focus and energy, and NPS that specifically address these needs are designed to bypass the testing menu of anti-doping laboratories. In addition, athletes may follow societal trends and may consume NPS for recreational purposes.

Based on their pharmacological properties, NPS can be divided into six groups [65]:

- Stimulants
- Opioids
- Synthetic cannabinoid receptor agonists
- Dissociatives
- Classic hallucinogens
- Sedatives/hypnotics

The World-Anti Doping Code defines the criteria to include a substance or method in the Prohibited List (the List): (1) evidence that it has the potential to enhance or enhances sport performance; (2) represents an actual or potential health risk to the athlete; and (3) violates the spirit of sport, reflecting the values found in and through sport. The three criteria have the same weight, and two out of three need to be fulfilled in order to consider whether the substance or a method should be prohibited [66]. From the aforementioned NPS groups, only three of them have a place in the List: stimulants, opioids and synthetic cannabinoid receptor agonists [33]. Dissociatives (e.g. phencyclidine (PCP) and ketamine), classic hallucinogens (e.g., LSD, psilocybin) and sedatives/hypnotics (e.g. benzodiazepines, barbiturates) are not prohibited in sport because they do not fulfil two of the three criteria established by the Anti-Doping Code. In this regard, these groups of substances are physically and mentally performance detrimental, and therefore their use is incompatible with sport practice and competition. While they certainly represent a risk for the health of the athlete, they would not be considered a violation of the spirit of sport since their abuse is linked to recreational purposes or addiction rather than sport practice. As a consequence, they are outside WADA's responsibilities. In addition, serotonin reuptake inhibitors and modulators and pure nootropics affecting memory are not prohibited, as there is no evidence that they provide an unfair advantage in sport. All PS are prohibited in-competition only, since it is considered that their effects are short-lived. Although it can be argued that these substances may be advantageous out-of-competition during the training period as well, and should be prohibited at all times, this possibility has not been considered for the moment. As of 2021, the Code defines that the in-competition period starts at 11:59 pm of the day before the competition that the athlete is scheduled to participate and finishes at the end of the competition with the sample collection process [67]. The List also identifies prohibited substances and methods as specified on non-specified with regard to the application of sanctions, which range from a reprimand to a maximum of 4 years' ineligibility for a first offence [33, 66]. In the case of specified substances or methods, it is considered that there is a possibility they were used by an athlete for a purpose other than the enhancement of sport performance. Examples of specified substances would be those generally available in over-the-counter medicinal products, present in foodstuff, used mainly for recreational purposes or because they are less likely to be successfully abused as doping agents. Among the three classes of PS in the List, only a number of stimulants are clearly identified as non-specified (Class S6.a). These are mainly classical PS widely and effectively abused for doping in sport. S6.a is closed, meaning that only the substances named belong to this subclass. All other stimulants (S6.b) as well as narcotics (S7) and

cannabinoids (S8) are specified substances [33]. The class of narcotics is also closed except with regard to fentanyl derivatives [33]. Specified stimulants (S6.b) and cannabinoids (S8) are open classes, meaning that only a number of examples are given in the List. Other drugs within the same category that are not named will fall into these categories by virtue of phrases such as "included but not limited" and "substances with similar chemical structure and/or similar biologic effect" to the ones listed. The purpose is twofold: (a) it would be practically not possible to name all substances existing worldwide within these categories, and (b) if a new substance comes onto the market, it will be automatically considered belonging to the class by virtue of its chemical structure and known or perceived pharmacological activity. Point (b) is particularly important for NPS, as any new designer drug will be covered within those categories as soon as WADA becomes aware of it and the chemical structure is verified, or the psychoactive effect inferred or reported. Any NP stimulant will automatically be classified as a specified stimulant. However, if WADA determines that the NPS has a profile that defines it as a non-specified stimulant (e.g., pharmacologically optimal for doping purposes, not available legally or over the counter), it will have to be included by name in the non-specified subclass. Since the List is updated every 1 January, the NP stimulant will temporarily be classified as specified during the course of the year and upgraded to non-specified by naming it in the S6.a section in the year that follows. All cannabinoids are specified substances, so all NPS in this class will be specified as well. Narcotics is a closed class, except for fentanyl and its derivatives, so any NPS that is derived from fentanyl will be automatically included. Any other type of narcotic NPS will need to be evaluated and included by name if it is deemed that it should be prohibited in sport. All drugs included in as narcotics are specified. The 2021 Code introduced the concept of "substances of abuse" [67], and the List will identify substances that are frequently abused in society outside of the context of sport. The 2021 List includes cocaine, diamorphine (heroin), methylenedioxymethamphetamine (MDMA/"ecstasy") and tetrahydrocannabinol (THC) [68]. This means that if an athlete can demonstrate that the use of any of these four substances was out-of-competition and unrelated to sport performance, the suspension imposed will be 3 months, with the possibility of reducing it to 1 month if the athlete completes a rehabilitation programme. Other drugs may be identified as "substances of abuse" in the future, but it is not expected that any NPS will be part of this group because there will be little data on the prevalence of use, the advantages offered in sports or their addiction potential. Evaluating the status of NPS is complex because very little is known about their effects. Not all PS are prohibited in sport as they must fulfil the criteria established in the Code. All NPS are potentially a risk for health (second criteria), as they are chemical products never tested for their safety profiles, produced in clandestine laboratories using unsophisticated techniques of synthesis and purification and prone to cross-contamination with other substances manufactured simultaneously. To define the potential performance-enhancing effect (first criteria) of an NPS, a first step is to determine the chemical structure to see if it fits any of the prohibited classes. For example, NP phenethylamines will mostly act as stimulants and be prohibited, but those containing methoxy groups on the two and five

positions of the benzene ring are most likely hallucinogenic and, if so, will not be considered prohibited substances in sport [69]. Therefore, a lot can be inferred from the chemical structure. The biologic effects, however, will be more difficult to ascertain. Unlike experimental drugs in preclinical or clinical studies, it is not possible to test the psychoactive effects in controlled human studies, and the rapidity by which these NPS appear and disappear from the market does not make them attractive candidates for study in animals or in vitro. It is possible to gather some information on their effects by browsing Internet forums, where users/athletes exchange information about enhanced sport performance, and from forensic or emergency ward reports. Nevertheless, as written in the List, it is necessary to show chemical similarity or biologic effect, and in the vast majority of cases, it is relatively straightforward to establish one or the other. This task was further facilitated in the 2015 List, which identified the whole family of phenethylamine derivatives as prohibited, to address the growing number of NPS designer drugs derived from this chemical.

Trends

Traditional PS commonly used for doping purposes are easily detected by routine doping control analysis. However, it is more challenging to tackle that analysis and identification of NPS, which are steadily flooding the market. The ready access to raw materials, the simple chemical reactions involved in NPS synthesis, which facilitate mass production, and the growing influence of the underworld in doping activities favour the continuous supply of these drugs. In order to avoid detection, the product labels either do not list the NPS or do so under a fake name or a false chemical structure in an attempt to deceive the user and to delay or mislead the development of proper detection methods. As the structure of most NPS is unknown, the identification relies, mainly, on untargeted or retrospective screening analysis of doping control samples, analysis of material seized by law enforcement or the proactive purchase of supplements through Internet providers for its identification and validation of detection methods.

Three major groups can be identified as NPS in dietary supplements used for doping purposes.

i. *Stimulants*

The NPS included in dietary supplements are mainly derived from the “classic” doping stimulants described above. The most common can be divided into two groups:

- Phenethylamine (PEA) derivatives: this group includes derivatives of classical stimulants such as amphetamines, cathinones and ephedrines. The phenethylamine core can be slightly altered to produce a wide array of compounds that differ, for example, in the nitrogen terminus, the presence of alkyl chains at the α-carbon and a number of different phenyl ring substitutions. These structural minor changes can significantly impact the mechanism of action of designer

phenethylamines, including monoamine release and/or reuptake inhibition, and the relative selectivity for the dopamine, norepinephrine and serotonin transporters [70–73]. The popularity of stimulants precedes the presence of this kind of NPS in supplements. They are routinely found in the analysis of products claiming to increase stamina as well as induce weight loss and are the source of numerous positive doping controls [34] as well as fatalities. Examples of these NPS include β-Methylphenethylamine (β-MePEA), α-Ethyl-phenethylamines (α-Ethyl-PEAs) and their derivatives [57, 74–79]. Synthetic cathinones such as mephedrone were first synthesised in the 1920s but remained largely unknown until they were rediscovered in the early twenty-first century. They were sold freely under names such as "bath salts", "plant food/fertilizers" or "research chemicals" and were at the time legal compounds. 3,4-Methylenedioxypyrovalerone (MDPV), a common synthetic cathinone, affects the brain in a manner similar to cocaine but is at least ten times more powerful [80]. Due to its link to several fatalities, MDPV and other synthetic cathinones have been recently classified as a controlled substance in some countries. However, synthetic cathinones are still readily available through the Internet in a wide array of replacement compounds with new chemical modifications in order to bypass law enforcement [81, 82].

- Aliphatic amines: the ban of 1,3-dimethylamylamine (methylhexaneamine) by sporting authorities led to an increase in the inclusion of similar aliphatic amines in supplements. Contrary to methylhexanamine, these new substances have never been approved as medications. These include 3-methylhexan-2-amine, 1,4-dimethylamylamine and 1,3-dimethylbutylamine [83–85]. Although octodrine (2-amino-6-methylheptane) cannot be technically considered an NPS, since it was commercialized in the past as a nasal decongestant, it has been recently reintroduced in the market of supplements, mainly targeting athletes [84].

ii. *Narcotics*

Despite the opioid and specifically the fentanyl crisis that has affected the world in recent years, it is not expected that these types of NPS will be purposely incorporated in dietary supplements targeting athletes. Fentanyl-derived NPS are 100 times more potent than morphine, so very low concentrations are needed to lethally overdose. This fact, combined with their addictive potential and side effects such as sedation, drowsiness, dizziness and respiratory depression, makes them rather incompatible and unattractive as components of sports dietary supplements.

To illustrate this point, mitragynine, an alkaloid with stimulant and opioid characteristics present in the plant product kratom, was included in the WADA Monitoring Program from 2014 to 2017, in order to determine patterns of abuse in athletes. Although mitragynine cannot be considered an NPS since it has been traditionally used in Southeast Asia, it has gained popularity as a dietary supplement in the western world in recent years [86–88]. However, the monitoring programme barely showed any use of mitragynine among the athletic population, further supporting that opioids NPS may not be of great concern in sports.

iii. *Cannabinoids*

Synthetic cannabinoids, such as “Spice”, “herbal incense” and “K2”, are man-made compounds that bind to the cannabinoid receptors, albeit with higher affinities when compared to tetrahydrocannabinol (THC) [89, 90]. While THC is metabolized to only one active metabolite, many NP synthetic cannabinoids metabolize to generate pharmacologically active metabolites prolonging the psychotropic effects of the parent compound and contributing to its toxicity. Although first synthesized in the mid-1960s, they became popular in the mid-2000s, as legal replacements to cannabis. Following reports of intoxications and deaths, Spice was banned, only to be replaced by other NP synthetic cannabinoids. Even though these products are mainly sold to be smoked, they are occasionally found in dietary supplements in the form of tablets, candies, cookies or liquids, usually mixed with other substances [91–93]. Although there is no solid evidence that these supplements are manufactured to enhance sport performance, they can certainly cause unintended doping when consumed for recreational purposes.

Prevention Strategies

The use of dietary supplements containing NPS by athletes is a serious concern, as a significant number of anti-doping rule violations have been attributed to the misuse of supplements [51, 94, 95]. Blaming a positive doping control to a poorly labelled dietary supplement is not an adequate defence in a doping hearing. The problems raised by NPS in supplements are globally twofold: those originating from the NPS themselves and those linked to the manufacturing of dietary supplements. The supplement industry is unregulated, and although the manufacturers are required to label their products, it is well known that discrepancies exist between ingredients listed on labels and the actual ingredients the products contain. The presence of NPS in a supplement could be intentional or could be due to subpar quality control during production. In addition, the lack of good manufacturing practices can lead to cross-contamination with other products in the manufacturing facility. This lack of regulation opens the door for fraudulent production of dietary supplements [96–102]. One way to deal with this problem is to regulate the supplement industry. However, this is within the jurisdiction and the will of the governments around the world, who are widely aware of the problem. With regard to sporting authorities, the best strategy lies with prevention achieved through education. This includes information offered via Internet access through the sports authorities’ websites, active campaigns, reaching out to athletes during sports events, publications or conferences, to name a few. Athletes should be made aware that the risks of taking supplements far outweigh the potential benefits. Another strategy to avoid contaminated supplements is the use of products that have been subjected to a quality assurance scheme. However, WADA is neither involved in the testing of dietary/nutritional supplements nor in any certification process and

therefore does not certify or endorse any products. In addition, the International Standard for Laboratories establishes that WADA-accredited laboratories cannot engage in analysing dietary supplements unless as part of a doping case investigation. Some third-party testers of supplements exist, and this may reduce the risk of contamination but not eliminate it. For example, even if one batch of a product is free of prohibited substances, there is no assurance that another batch will not be contaminated if the source of material and manufacturing practices are not controlled [100, 102–104]. However, regulating the supplement industry will only address part of the problematic of NPS in supplements. Many of the products originate from clandestine laboratories that are part of criminal rings dedicated to the production, smuggling and distribution of these products. Law enforcement authorities play a key role in identifying and clamping down these activities either through intelligence and investigations, seizures during raids or at border controls. However, once the NPS-containing supplement reaches the market, it is necessary to identify their presence both in the supplements and in the doping controls. While the approach of targeted screening for prohibited compounds or their metabolites in blood or urine is an effective approach for doping control, it has its limitations. In this regard, NPS are designer drugs intended to bypass targeted drug or doping control analysis, so a more untargeted approach is needed. Detection and identification of these substances, be it from seized material, online purchases, doping controls or forensic samples, is a major challenge. Therefore, once an NPS is identified, it is fundamental that the information is shared. Among the most comprehensive databases on NPS, the United Nations Office of Drug Control has developed the Early Warning Advisory portal that provides open access to basic information on these substances and, to registered users, specific information on their chemical structures and laboratory analysis [64, 65]. Other examples of information gathering include the National Forensic Laboratory Information System (NFLIS) as part of the Drug Enforcement Administration (DEA) programme that collect results of forensic analyses, the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) and the Inter-American Drug Abuse Control Commission (CICAD) [105–107]. Rapid access to information allows taking immediate preventive measures for NPS that may pose an immediate health threat to consumers and developing the appropriate analytical methods for early detection, to prevent widespread undetected use of these compounds.

Conclusion

The alarming production of NPS combined with the unregulated manufacturing of nutritional supplements targeted for athletes is a serious combination that should be tackled from different angles. The rapid response by anti-doping authorities to the appearance of an NPS that is not covered by anti-doping regulations or by the laboratories testing menus results in the synthesis and production of another NPS to once more start the cycle. The maintenance of and access to databases storing

information on NPS are important elements to address the problem of these drugs in supplements. In addition, a tight and fluid interaction and exchange of information between government agencies, anti-doping organizations, law enforcement, analytical laboratories and researchers in the field, through scientific meetings, publications, articles or working groups, will certainly make this challenging task more efficient. In addition, pressure should be put on the authorities to regulate the industry manufacturing dietary supplements. Finally, athletes, who are the end consumer of these supplements, should be constantly reminded of the high risks of using these products, as they not only take a chance of producing a positive doping control test but are jeopardizing their health administering products that have not been subjected to preclinical studies. Through education, the demand should decrease, and if combined with a better controlled supplement industry and an effective NPS tracking and identification system, the difficulty of controlling NPS in supplements should be reduced to a minimum.

Acknowledgements I would like to thank Elizabeth Adams for helpful suggestions and proofreading.

References

1. Karunamoorthi K, Jegajeevanram K, Vijayalakshmi J, Mengistie E (2013) Traditional medicinal plants: a source of Phytotherapeutic modality in resource-constrained health care settings. J Evid Based Compl Altern Med 18:67–74
2. Fabricant D, Fansworth NR (2001) The value of plants used in traditional medicine for drug discovery. Environ Heath Perspect 109(Suppl 1):69–75
3. Falzon C, Balabanova A (2017) Phytotherapy: an introduction to herbal medicine. Prim Care 44:217–227
4. Bamola N, Verma P, Negi C (2018) A review on some traditional medicinal plants. Int J Life Sci Scienti Res 4:1550–1556
5. Sen T, Samanta SK (2015) Medicinal plants, human health and biodiversity: a broad review. Adv Biochem Eng Biotechnol 147:59–110
6. Taylor JLS, Rabe T, McGaw LJ, Jäger AK, van Staden J (2001) Towards the scientific validation of traditional medicinal plants. Plant Growth Reg 34:23–47
7. Shorter W, Kathryn Segesser K (2013) Traditional Chinese medicine and Western psychopharmacology: building bridges. Phytother Res 27:1739–1744
8. Campbel R, Young SP (2014) Central nervous system stimulants: basic pharmacology and relevance to anaesthesia and critical care. Anaesth Intensive Care Med 16:21–25
9. Patocka J (2015) Strychnine. In: Gupta RC (ed) Handbook of toxicology of chemical warfare agents, 2nd edn. Elsevier Inc, Amsterdam, pp 215–222
10. Henry TA (1949) The plant alkaloids, 4th edn. J & A Churchill
11. Taylor DA (2003) Central nervous system stimulants. In: IV Drugs affecting the central nervous system
12. Norn S, Kruse PR (2004) Cardiac glycosides: from ancient history through Withering's foxglove to endogeneous cardiac glycosides. Dan Medicinhist Arbog:119–132

13. Stolberg VB (2011) The use of coca: prehistory, history, and ethnography. J Ethnicity Subs Abuse 10:126–146
14. Lyon PJ (2004) The more things change. Latin Am Anthropol Rev 6:29–32
15. Presley CC, Lindsley CW (2018) DARK classics in chemical neuroscience: opium, a historical. Perspective ACS Chem Neurosci 9:2503–2518
16. Cassels BK, Sáez-Briones P (2018) Dark classics in chemical neuroscience: mescaline. ACS Chem Neurosci 9:2448–2458
17. Blainey MG (2015) Forbidden therapies: Santo Daime, Ayahuasca, and the prohibition of entheogens in Western society. J Relig Health 54:287–302
18. Geiger HA, Wurst MG, Daniels RN (2018) DARK classics in chemical neuroscience: psilocybin. ACS Chem Neurosci 9:2438–2447
19. Wasko MJ, Witt-Enderby PA, Surratt CK (2018) DARK classics in chemical neuroscience: Ibogaine. ACS Chem Neurosci 9:2475–2483
20. Chowdhury AN (1995) Drug abuse and eco-stress adaptation. Addiction 90:19–20
21. Kamienski L (2016) Shooting up. A short history of drugs and war. Oxford University Press, pp 31–304
22. Rasmussen N (2011) Medical science and the military: the Allies' use of amphetamine during world war II. J Interdiscip Hist 42:205–233
23. Defalque RJ, Wright AJ (2011) Methamphetamine for Hitler's Germany: 1937 to 1945. Bull Anesth Hist 29:21–24
24. Zvejniece L, Svalbe B, Veinberg G, Grinberga S, Vorona M, Kalvinsh I, Dambrova M (2011) Investigation into stereoselective pharmacological activity of phenotropil. Basic Clin Pharmacol Toxicol 109:407–412
25. Pedersen W, Sandberg S, Copes H (2015) High speed: amphetamine use in the context of conventional culture. Deviant Behav 36:146–165
26. Lakhan SE, Kirchgessner A (2012) Prescription stimulants in individuals with and without attention deficit hyperactivity disorder: misuse, cognitive impact, and adverse effects. Brain Behav 2:661–677
27. Yesalis CE, Bahrke MS (2002) History of doping in sport. In: Bahrke MS, Yesalis CE (eds) Performance-enhancing substances in sport and exercise. Human Kinetics, Champaign, IL, pp 1–20
28. Abbott K (2012) The 1904 Olympic Marathon may have been the strangest ever. Smithsonian Magazine, August 7 2012 https://wwwsmithsonianmagcom/history/the-1904-olympic-marathon-may-have-been-the-strangest-ever-14910747 Accessed 13 Oct 2020
29. Baron DA, Reardon CL, Baron SH (2013) Doping in sport. In: Baron DA, Reardon CL, Baron SH (eds) Clinical sports psychiatry: an international perspective. Wiley, Oxford, UK, pp 18–32
30. Verroken M (2000) Drug use and abuse in sport. Bailliere's Clin Endocrinol Met 14:1–23
31. Annex VIII (1968) Doping, report of the medical commission, minutes of the 66th session of the International Olympic Committee. New Town Hall, Grenoble, February 1–5
32. World Anti-Doping Agency. List of prohibited substances and methods (2004). https://www.wada-ama.org/sites/default/files/resources/files/WADA_Prohibited_List_2004_EN.pdf. Accessed 13 Oct 2020
33. World Anti-Doping Agency. List of prohibited substances and methods. (2020). https://www.wada-ama.org/sites/default/files/wada_2020_english_prohibited_list_0.pdf. Accessed 13 Oct 2020
34. World Anti-Doping Agency. Anti-Doping Testing Figures Report 2006–2018. https://www.wada-ama.org/en/resources/laboratories/anti-doping-testing-figures-report. Accessed 13 Oct 2020
35. Gurley BJ, Gardner SF, White LM, Wang PL (1998) Ephedrine pharmacokinetics after the ingestion of nutritional supplements containing Ephedra sinica (Ma Huang). Ther Drug Monit 20:439–445
36. Lee MR (2011) The history of ephedra (ma-huang) J Roy Coll Phys Edinburgh 41:78–84

37. Morton SC (2005) Ephedra. Stat Sci 20:242–248
38. Roman MC (2004) Determination of ephedrine alkaloids in botanicals and dietary supplements by HPLC-UV: collaborative study. J AOAC Int 87:1–14
39. Chang CW, Hsu SY, Huang GQ, Hsu MC (2018) Ephedra alkaloid contents of Chinese herbal formulae sold in Taiwan. Drug Test Anal 10:350–356
40. Miller SC (2004) Safety concerns regarding ephedrine-type alkaloid-containing dietary supplements. Military Med 169:87–93
41. Josefson D (1996) Herbal stimulant causes US deaths. Br Med J 312:1378–1379
42. Doyle H, Kargin M (1996) Herbal stimulant containing ephedrine has also caused psychosis. Br Med J 313:756
43. Ault A (1997) FDA proposes limits on ephedrine supplements. Lancet 349:1753
44. Nightingale SL (1996) Warning issued about the street drugs containing botanical sources of ephedrine. JAMA 275:1534
45. Haller C, Benowitz N (2000) Adverse cardiovascular and central nervous system events associated with dietary supplements containing ephedra alkaloids. N Engl J Med 343:1833–1838
46. Onakpoya IJ, Heneghan CJ, Aronson JK (2016) Post-marketing withdrawal of anti-obesity medicinal products because of adverse drug reactions: a systematic review. BMC Med 14:191–202
47. Lee MK, Cheng BWH, Che CT, Hsieh DPH (2000) Cytotoxicity assessment of Ma-huang (*Ephedra*) under different conditions of preparation. Toxicol Sci 56:424–430
48. Knight J (2004) Safety concerns prompt US ban on dietary supplement. Nature 427:90
49. Rocha T, Amaral JS, Oliveira MBPP (2016) Adulteration of dietary supplements by the illegal addition of synthetic drugs: a review. Comprehensive Rev Food Sci Food Safety 15:43–62
50. Wabe NT (2011) Chemistry, pharmacology, and toxicology of Khat (Catha Edulis Forsk): a review. Addict Health 3:137–149
51. Ros JJ, Pelders MG, De Smet PA (1999) A case of positive doping associated with a botanical food supplement. Pharm World Sci 21:44–46
52. (1950) New and nonofficial remedies: methylhexamine; Forthane. JAMA 143:1156
53. Lisi A, Hasick N, Kazlauskas R, Goebel C (2011) Studies of methylhexaneamine in supplements and geranium oil. Drug Test Anal 3:873–876
54. Elsohly MA, Gul W, Elsohly KM, Murphy TP, Weerasooriya A, Chittiboyina AG, Avula B, Khan I, Eichner A, Bowers LD (2012) Pelargonium oil and methyl hexaneamine (MHA): analytical approaches supporting the absence of MHA in authenticated *Pelargonium graveolens* plant material and oil. J Anal Toxicol 36:457–471
55. ElSohly MA, Gul W, Tolbert C, ElSohly KM, Murphy TP, Avula B, Chittiboyina AG, Wang M, Khan IA, Yang M, Guo D, Zhang WD, Su J (2015) Methylhexanamine is not detectable in Pelargonium or Geranium species and their essential oils: a multi-Centre investigation. Drug Test Anal 7:645–654
56. Austin KG, Travis J, Pace G, Lieberman HR (2014) Analysis of 1,3 dimethylamylamine concentrations in Geraniaceae, geranium oil and dietary supplements. Drug Test Anal 6:797–804
57. Pawar RS, Grundel E (2017) Overview of regulation of dietary supplements in the USA and issues of adulteration with phenethylamines (PEAs). Drug Test Anal 9:500–517
58. Venhuis B, Keizers P, van Riel A, de Kaste D (2014) A cocktail of synthetic stimulants found in a dietary supplement associated with serious adverse events. Drug Test Anal 6:578–581
59. Pawar RS, Sagi S, Leontyev D (2020) Analysis of bitter orange dietary supplements for natural and synthetic phenethylamines by LC-MS/MS. Drug Test Anal. https://doi.org/10.1002/dta.2871
60. Pohl K, Kriech W (1991) Therapy of orthostatic disorders of cardiovascular regulation. Placebo controlled double-blind study with oxilofrine. Fortschr Med 109:685–688
61. Yuen YP, Lai CK, Poon WT, Ng SW, Chan AY, Mak TW (2007) Adulteration of over-the-counter slimming products with pharmaceutical analogue-an emerging threat. Hong Kong Med J 13:216–220

62. De Carvalho LM, Cohen PA, Silva CV, Moreira APL, Falcao TM, Dal Molin TR, Zemolin G, Martini M (2012) A new approach to determining pharmacologic adulteration of herbal weight loss products. Food Addit Contam A 29:1661–1667
63. Park S, Lee JG, Roh SH, Kim G, Kwon CH, Park HR, Kwon KS, Kim D, Kwon SW (2012) Determination of PDE-5 inhibitors and appetite suppressants in adulterated dietary supplements using LC/PDA and LC/MS. Food Addit Contam B 5:29–32
64. UNODC Early warning advisory on new psychoactive substances. What are NPS? https://www.unodc.org/LSS/Page/NPS#:~:text=UNODC%20uses%20the%20term%20%E2%80%9Cnew,pose%20a%20public%20health%20threat%E2%80%9D. Accessed 13 Oct 2020
65. UNODC Early warning advisory on new psychoactive substances. pharmacology. https://www.unodc.org/LSS/Page/NPS/pharmacology Accessed 13 Oct 2020
66. World Anti-Doping Agency. World Anti-Doping Code 2015. https://www.wada-ama.org/sites/default/files/resources/files/wada_anti-doping_code_2019_english_final_revised_v1_linked.pdf Accessed 13 Oct 2020
67. World Anti-Doping Agency. World Anti-Doping Code 2021 https://www.wada-ama.org/sites/default/files/resources/files/2021_wada_code.pdf Accessed 13 Oct 2020
68. World Anti-Doping Agency. List of prohibited substances and methods. (2021). https://www.wada-ama.org/sites/default/files/resources/files/2021list_en.pdf Accessed 13 Oct 2020
69. Fantegrossia WE, Murnanea AC, Reissigb CJ (2008) The behavioral pharmacology of hallucinogens. Biochem Pharmacol 75:17–33
70. Zamberlan F, Sanz C, Martínez Vivot R, Pallavicini C, Erowid F, Erowid E, Tagliazucchi E (2018) The varieties of the psychedelic experience: a preliminary study of the association between the reported subjective effects and the binding affinity profiles of substituted phenethylamines and tryptamines. Front Integrative Neurosci 12:1–22
71. Calinski DM, Kisor DF, Sprague JE (2019) A review of the influence of functional group modifications to the core scaffold of synthetic cathinones on drug pharmacokinetics. Psychopharmacol (Berl) 236:881–890
72. Peters FT, Martinez-Ramirez JA (2010) Analytical toxicology of emerging drugs of abuse. Ther Drug Monit 32:532–539
73. King LA (2014) New phenethylamines in Europe. Drug Test Anal 6:808–818
74. El Sohly MA, Gul W (2014) LC–MS-MS analysis of dietary supplements for N-ethyl-a-ethyl-phenethylamine (ETH), N, N-diethylphenethylamine and phenethylamine. J Anal Toxicol 38:63–72
75. Kwiatkowska D, Wójtowicz M, Jarek A, Goebel C, Chajewska K, Turek-Lepa E, Pokrywka A, Kazlauskas R (2015) N,N-dimethyl-2-phenylpropan-1-amine – new designer agent found in athlete urine and nutritional supplement. Drug Test Anal 7:331–335
76. Wójtowicz M, Jarek A, Chajewska K, Turek-Lepa E, Kwiatkowska D (2015) Determination of designer doping agent--2-ethylamino-1-phenylbutane--in dietary supplements and excretion study following single oral supplement dose. J Pharm Biomed Anal 115:523–533
77. Wójtowicz M, Jarek A, Chajewska K, Kwiatkowska D (2016) N,N-dimethyl-2-phenylpropan-1-amine quantification in urine: application to excretion study following single oral dietary supplement dose. Anal Bioanal Chem 408:5041–5047
78. Uralets V, App M, Rana S, Morgan S, Ross W (2014) Designer phenethylamines routinely found in human urine: 2-ethylamino-1-phenylbutane and 2-amino-1-phenylbutane. J Anal Toxicol 38:106–109
79. Cohen PA, Travis JC, Venhuis BJ (2014) A methamphetamine analog (N,-diethylphenylethylamine) identified in a mainstream dietary supplement. Drug Test Anal 6:805–807
80. Baumann MH, Walters HM, Niello M, Sitte HH (2018) Neuropharmacology of synthetic cathinones. Handb Exp Pharmacol 252:113–142
81. Riley AL, Nelson KH, To P, López-Arnau R, Xu P, Wang D, Wang Y, Shen HW, Kuhn DM, Angoa-Perez M, Anneken JH, Muskiewicz D, Hall FS (2020) Abuse potential and toxicity of the synthetic cathinones (i.e., "Bath salts"). Neurosci Biobehav Rev 110:150–173

82. Majchrzak M, Celiński R, Kuś P, Kowalska T, Sajewicz M (2018) The newest cathinone derivatives as designer drugs: an analytical and toxicological review. Forensic Toxicol 36:33–50
83. Cohen PA, Travis JC, Venhuis BJ (2015) A synthetic stimulant never tested in humans, 1,3-dimethylbutylamine (DMBA), is identified in multiple dietary supplements. Drug Test Anal 7:83–87
84. Cohen PA, Travis JC, Keizers PJH, Deuster P, Venhuis BJ (2018) Four experimental stimulants found in sports and weight loss supplements: 2-amino-6-methylheptane (octodrine), 1,4-dimethylamylamine (1,4-DMAA), 1,3-dimethylamylamine (1,3-DMAA) and 1,3-dimethylbutylamine (1,3-DMBA). Clin Toxicol (Phila) 56:421–426
85. Riley PA (2012) DMAA as a dietary supplement ingredient. Arch Intern Med 172:1038–1039
86. Han C, Schmitt J, Gilliland KM (2020) DARK classics in chemical neuroscience: Kratom. ACS Chem Neurosci. doi: https://doi.org/10.1021/acschemneuro.9b00535
87. Mudge EM, Brown PN (2018) Determination of alkaloids in *Mitragyna speciosa* (Kratom) raw materials and dietary supplements by HPLC-UV: single-laboratory validation, first action 2017.14. J AOAC Int 101:964–965
88. Chien GCC, Odonkor C, Amorapanth P (2017) Is Kratom the new 'legal high' on the block?: the case of an emerging opioid receptor agonist with substance abuse potential. Pain Phys 20:E195–E198
89. Alipour A, Patel PB, Shabbir Z, Gabrielson S (2019) Review of the many faces of synthetic cannabinoid toxicities. Ment Health Clin 9:93–99
90. Walsh KB, Andersen HK (2020) Molecular pharmacology of synthetic cannabinoids: delineating CB1 receptor-mediated cell signaling. Int J Mol Sci. https://doi.org/10.3390/ijms21176115
91. Heo S, Yoo GJ, Choi JY, Park HJ, Do JA, Cho S, Baek SY, Park SK (2016) Simultaneous analysis of cannabinoid and synthetic cannabinoids in dietary supplements using UPLC with UV and UPLC–MS-MS. J Ana Toxicol 40:350–359
92. Choi H, Heo S, Choe S, Yang W, Park Y, Kim E, Chung H, Lee J (2013) Simultaneous analysis of synthetic cannabinoids in the materials seized during drug trafficking using GC-MS. Anal Bioanal Chem 405:3937–3944
93. Rianprakaisang T, Gerona R, Hendrickson RG (2020) Commercial cannabidiol oil contaminated with the synthetic cannabinoid AB-FUBINACA given to a pediatric patient. Clin Toxicol (Phila) 58:215–216
94. Parr MK, Pokrywka A, Kwiatkowska D, Schänzer W (2011) Ingestion of designer supplements produced positive doping cases unexpected by the athletes. Biol Sport 28:153–157
95. US Anti-Doping Agency. Case studies and arbitration decisions. https://www.usada.org/athletes/substances/supplement-411/realize-safety-issues-exist/case-studies-arbitration-decisions/ Accessed 14 Oct 2020
96. Walpurgis K, Thomas A, Geyer H, Mareck U, Thevis M (2020) Dietary supplement and food contaminations and their implications for doping controls. Foods. https://doi.org/10.3390/foods9081012
97. Martínez-Sanz JM, Sospedra I, Ortiz CM, Baladía E, Gil-Izquierdo A, Ortiz-Moncada R (2017) Intended or unintended doping? A review of the presence of doping substances in dietary supplements used in sports. Nutrients 9:1093. https://doi.org/10.3390/nu9101093
98. Geyer H, Parr MK, Koehler K, Mareck U, Schänzer W, Thevis M (2008) Nutritional supplements cross-contaminated and faked with doping substances. J Mass Spectrom 43:892–902
99. Kohler M, Thomas A, Geyer H, Petrou M, Schänzer W, Thevis M (2010) Confiscated black market products and nutritional supplements with non-approved ingredients analyzed in the Cologne doping control laboratory 2009. Drug Test Anal 2:533–537
100. Attipoe S, Cohen PA, Eichner A, Deuster PA (2016) Variability of stimulant levels in nine sports supplements over a 9-month period. Int J Sport Nutr Exerc Metab 26:413–420
101. Uchiyama N, Matsuda S, Kawamura M, Kikura-Hanajiri R, Goda Y (2014) Identification of two new-type designer drugs, piperazine derivative MT-45 (I-C6) and synthetic peptide

Noopept (GVS-111), with synthetic cannabinoid A-834735, cathinone derivative 4-methoxy-α-PVP, and phenethylamine derivative 4-methylbuphedrine from illegal products. Forensic Toxicol 32:9–18
102. Australian Sports Anti-Doping Authority Supplements in sport. https://www.asada.gov.au/substances/supplements-sport Accessed 14 Oct 2020
103. UK Anti-Doping Managing supplements risks. https://www.ukad.org.uk/athletes/managing-supplement-risks Accessed 14 Oct 2020
104. de Hon O, Coumans B (2007) The continuing story of nutritional supplements and doping infractions. Br J Sports Med 41:800–805
105. Drug Enforcement Administration. National Forensic Laboratory Information System. https://www.nflis.deadiversion.usdoj.gov/ Accessed 14 Oct 2020
106. European Monitoring Centre for Drugs and Drug Addiction. https://www.emcdda.europa.eu/ Accessed 14 Oct 2020
107. Inter-American Drug Abuse Control Commission. http://www.cicad.oas.org/main/default_eng.asp Accessed 14 Oct 2020