Psychoactive natural products: overview of recent developments

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Abstract

Natural psychoactive substances have fascinated the curious mind of shamans, artists, scholars and laymen since antiquity. During the twentieth century, the chemical composition of the most important psychoactive drugs, that is opium, cannabis, coca and "magic mushrooms", has been fully elucidated. The mode of action of the principal ingredients has also been deciphered at the molecular level. In the past two decades, the use of herbal drugs, such as kava, kratom and *Salvia divinorum*, began to spread beyond their traditional geographical and cultural boundaries. The aim of the present paper is to briefly summarize recent findings on the psychopharmacology of the most prominent psychoactive natural products. Current knowledge on a few lesser-known drugs, including bufotenine, glaucine, kava, betel, pituri, lettuce opium and kanna is also reviewed. In addition, selected cases of alleged natural (or semi-natural) products are also mentioned.

O, mickle is the powerful grace that lies
In herbs, plants, stones, and their true qualities
William Shakespeare *(Romeo and Juliet)*

INTRODUCTION

During the past 200 years, there has been major progress in our understanding of the composition and effects of many psychoactive natural products, particularly those that have therapeutic uses. This article reviews the pharmacohistory, the chemistry, the mode of action, and, where pertinent, the toxicology of some globally emerging and some lesser-known psychoactive natural products with emphasis on recent findings. Some of these substances or potions have been known for decades but became popular on the recreational drug scene only recently; the prevalence and extent of their use, however, are not captured by regular epidemiological questionnairs. Others appear to have only marginal use, yet they provide an interesting insight into how new drugs emerge from obscurity. Some of the substances were detected for the first time in Europe and reported to the Early warning system (EWS) of the European Monitoring Centre for Drugs and Drug Addiction as a "new psychoactive substance"[1] just recently. Regulatory aspects are only briefly mentioned since drug legislation varies from country to country and is currently undergoing dynamic changes.

Historical background of psychoactive natural products research

The biochemical machinery of an organism generates many structurally related chemicals (Nature's "combinatorial library") of which some have physiological or ecological relevance, aiding survival of the producer in a hostile environment. For mankind, natural[2] products also represent an ancient and rich source of bioactive substances [1].

The unique psychoactivity of these drugs has fascinated shamans, artists, writers, scholars and laymen alike since antiquity. Through a lengthy, and sometimes dangerous, process of trial and error each culture discovered and developed a natural product-based tradition of "mind altering". In modern societies, the most extensively produced and widely consumed psychoactive drugs, that is alcoholic beverages, caffeine-containing drinks and tobacco products are all of natural origin.

Psychoactive natural products display an astonishing structural diversity and may come from three sources: plants, microorganisms or animals. According to estimates, the number of plants with proven or reputed psychoactivity exceeds 300 [2]; a recent compendium by the European Food Safety Authority lists hundreds of addictive or psy-

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1. European Council Decision 2005/387/JHA stipulates a "new psychoactive substance" as a new narcotic or psychotropic drug, in pure form or in preparation, that is not controlled by the relevant 1961 or 1971 United Nations Conventions. However, a new mode of use of a known "traditional" drug is often brought to the attention of the EWS of EMCDDA and relevant data are deposited in a new drugs database.

2. According to the Oxford Dictionary, the adjective "natural" refers to something that exists in or is derived from nature; not made or caused by humankind. The word "natural" is often, but erroneously, thought to be equivalent to "good" or "pure" as if many poisons, including nicotine, strychnine and botulinum toxin, were not products of nature.

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choactive botanical preparations [3]. The hallucinogenic properties of mushrooms have been known for millennia and over 200 fungal species that produce psychotropic substances have been described [4]. However, there are only sporadic reports on psychic effects elicited by deliberate or accidental ingestion of animals [5, 6] (for toads, see later).

The bioactive extracts obtained from an organism by self-experiments or biochemical and receptor-based screening methods are typically suites of structurally related chemicals interacting with a wide variety of biological targets. Furthermore, any single component of such a "chemical shotgun" may have more than one molecular target. In addition, one constituent may have high receptor affinity but low efficacy to elicit significant pharmacological response, while an other, sometimes minor, component may have low affinity but high efficacy thus the relevant pharmacological effect manifests only at a high dose (see, *e.g.,* [7]). Therefore, the overall psychosomatic response is complex and dose-dependent and this explains the versatility of many ethnobotanical preparations.

It has often been observed that the psychic and somatic effects of a natural preparation differ from those of the pure main ingredients indicating that minor constituents contribute to or modulate the activity of the major component. Mixtures containing synergistically acting ingredients pose methodological difficulties: bioassays using purified samples might miss the activity observed for the crude extract.

The isolation of the alkaloid morphine from opium by Sertürner six generations ago (1805) laid the foundation of phytochemistry and modern pharmacy. Further research on opioids culminated on one hand in the chemical total synthesis of morphine in 1952 and, on the other, in the discovery of endogenous opioid peptides and their receptors in the 1970s. Building on the results of these investigations, many (semi-)synthetic analgesics, cough suppressants, antidiarrheal agents as well as molecular probes for mode of action studies have been developed [8]. Heroin, oxycodone, desomorphine, naloxone, pethidine, methadone, the fentanils, dextromethorphan, loperamide, and ketazocine have become "household names" not only among specialists of medicine but also among those working in the broad field of addiction. Subsequently, the active principles of other natural psychoactive agents were also elucidated and, as shown in *Table 1*, the "Golden Area" of psychoactive natural products discovery appears to have lasted for almost two centuries.

A note of caution regarding olden literature: several chemicals have been isolated from exotic drugs. Yet, recent phytochemical re-analysis of many such plants detected these substances in trace amounts only (< 0.1%), a concentration unlikely to elicit the reported effects of the preparation. In other instances, the activity of an isolated substance was not verified in bioassays. In these cases the genuine bioactive component awaits identification. Publications solely relying on early literature thus must be assessed critically.

MAJOR EMERGING PSYCHOACTIVE NATURAL PRODUCTS
Khat

Khat refers to the evergreen shrub *Catha edulis* indigenous to East Africa. Khat also refers to the leaves and shoots of the plant chewed to provide mild stimulant effects. Khat has a variety of regional names such as mairungi (Uganda), miraa (Kenya), qat (Yemen), or tschat (Ethiopia

and Somalia). The shrub is an intensively cultivated, high-income cash crop in East Africa and the southwestern part of the Arabian Peninsula. In addition to supplying domestic markets, fresh khat bundles, each weighing 250-300 g, are nowadays shipped by airfreight into Europe, Australia and North America to ethnic groups immigrated from countries where khat-chewing is a tradition [9-13]. During the daily 3-6 hour-long afternoon chewing sessions, at least one bundle is consumed, mainly in social setting, to provide euphoric and stimulant affects. The number of regular, predominantly male, khat consumers is at least ten million although epidemiological data are lacking.

Several types of compounds have been isolated from khat, including amino acids, ascorbic acid, flavonoids, phenylalkylamine alkaloids, sesquiterpene polyester alkaloids (cathedulins), steroids, tannins, and terpenoids. The main psychoactive constituent was identified in 1975 and named cathinone *(Figure 1)* [14]. The cathinone-content of the leaves typically ranges from 0.04 to 0.3 %. Biosynthetically related alkaloids also present in khat are cathine (*i.e.*, norpseudoephedrine) *(Figure 1)*, and norephedrine, though they are only slightly active. Data on the bioactivity of other khat constituents are scarce.

Cathinone is a chemically unstable aminoketone. In the leaves it undergoes enzymatic reduction into cathine (*e.g.*, [15]), thus the harvested shoots lose psychoactivity within 2-3 days explaining the chewers' preference for fresh khat (see, *e.g.*, [16]). Interestingly, the chemical synthesis of racemic "cathinone" by Schmidt in 1889 preceded by many decades the identification of the natural product; its tendency to undergo decomposition was also noted a century ago.

Khat and its main ingredients are amphetamine-like dopaminergic psychostimulants with peripheral sympathomimetic effects [17, 18]. In the central nervous system, cathinone inhibits the reuptake of dopamine and norepinephrine into presynaptic nerve terminals without affecting serotonin transport [19]. Several reports indicate that khat use may lead to dependence, induce psychoses and cause cardiovascular diseases [20-23], but robust information on the somatic and mental health problems associated with regular use is lacking. Due to intensive farming of the plant, pesticides may contaminate the bundles [24] although the health consequences of such contamination have not been investigated. The environmental, socio-economic and health problems associated with the production and use of khat have recently become a focus of scientific and political debates [25, 26][3]. While cathinone and cathine are scheduled according to the UN Convention on Psychotropic Substances of 1971, khat leaves do not fall under any international regulatory system. Yet, Australia, several US states and European countries have recently introduced measures to control the trade of *Catha edulis* [9, 27].

It is interesting to follow the chronology of appearances of such aminoketone stimulants: first, in the late 1970s, the semi-synthetic methcathinone, *i.e.*, the *N*-methyl derivative of cathinone (also called ephedrone indicating that it is made by oxidizing ephedrine) appeared on the drugs scene in the then-Soviet Union; a decade later, in 1989, methcathinone was introduced into Michigan [28]; a decade lat-

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3. See also presentations of a conference organized by the European Science Foundation in Linköping, 5-9 October, 2009. Available from: www.esf.org/serving-science/conferences/details/2009/confdetail274/presentations.html.
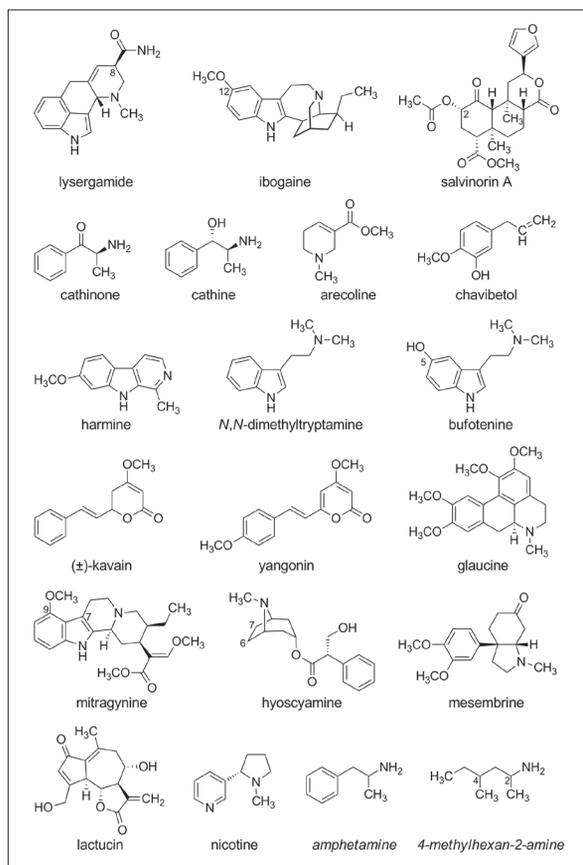
Figure 1

Chemical structure and common name of psychoactive substances of natural origin (a name in *italics* indicates a most likely man-made compound).

hallucinogen: inhalation of the vapors of doses equivalent to 200-500 microgram pure salvinorin A elicits strong hallucinations with virtually no discernible somatic effects. This dose is comparable to the effective oral dose of the semi-synthetic LSD (lysergic acid diethylamide) (100 microgram) or the synthetic DOB (4-bromo-3,5-dimethoxy-phenylisopropylamine) (1000 microgram), although the subjective effects are qualitatively different from those of any other known hallucinogens [32, 35-37]. The short duration of the effects is explained by the rapid, esterase-catalyzed hydrolysis of the 2-O-acetate of salvinorin A to its inactive alcohol (salvinorin B) [38, 39].

Unlike classical hallucinogens that target serotonin (5-HT) receptors, $5-HT_{2A}$-type in particular [40], salvinorin A acts as a selective κ-opioid receptor agonist [41, 42], as corroborated by recent X-ray crystal structure studies [43]. The analgesic and antiinflammatory activities of salvinorin A are of particular interest [44, 45]. There is also intensive research to explore the therapeutic potential of structurally related opioid receptor agonists or antagonists [46, 47]. For example, the hydrolytically stable salvinorin B 2-O-ethoxymethyl ether is several-fold more active as a κ-opioid receptor ligand than the natural product [48]; users' experience reports indicate that this semi-synthetic ether, named "Symmetry", is at least as potent as salvinorin A[5]. Interestingly, replacement of the 2-O-acetyl group of salvinorin A with a benzoyl group provides salvinorin B 2-O-benzoate (herkinorin), which is, in turn, a selective μ-opioid receptor agonist with antinociceptive activity *in vivo* [49, 50].

Preliminary experiments indicated low rodent toxicity [51] but no other study has examined the acute or chronic physiological adverse effects of *Salvia divinorum* leaves or extracts.

The vegetatively propagated plant as well as dried leaf preparations, often enriched with extracts from other *S. divinorum* leaves, are widely available but pure salvinorin A is rarely encountered. Analyses of *Salvia* leaf samples obtained from various vendors indicated large variations in salvinorin A content (0.13-5.0 mg/g) [52, 53]. The plant and/or salvinorin A are controlled in an increasing number of countries.

er it reappeared in several countries. Around the same time, in 2003, synthetic cathinone containing capsules ("Hagigat") were beginning to be sold in kiosks in Israel [29]. In retrospect, these appearances seem to have been preludes to the subsequent alarming emergence of synthetic cathinones (commonly referred to as "bath salts").

Salvia divinorum

The psychoactive mint *Salvia divinorum*, or the diviner's sage, is indigenous to the highlands of the Oaxaca state in Mexico, where Mazatec shamans have been using it for medical purposes, in healing ceremonies and divinatory rituals. Traditionally, the fresh leaves are chewed or pressed to make a drink. Since the late 1990s, the "recreational" use of *S. divinorum* as an herbal hallucinogen has been spreading globally especially among young adults [30, 31][4]. For this purpose, 0.25-0.75 grams of crushed dried leaves are smoked from a pipe or water bong to provide profound hallucinations and unique, "out-of-body" experiences that commence within a minute and last for 15-20 minutes [32, 33].

The psychoactive principle of the leaves is salvinorin A *(Figure 1)*. This non-nitrogenous, neoclerodane diterpene was isolated first by Ortega *et al.* in 1982. Independently, in 1984, the same compound was isolated and biologically characterized by Valdes *et al.*, who called it "divinorin A". Salvinorin A has not been detected in any other *Salvia* species examined to date [34]. It is the most potent natural

Lysergamide

The discovery and psychopharmacology of LSD (from the German "Lysergsäure-diäthylamid") have been well documented [54, 55]. LSD is a semi-synthetic compound usually prepared from lysergic acid, which is obtained hydrolytically from ergot alkaloids produced for the pharmaceutical industry by fermentation of *Claviceps fungi*. Lysergamide (LSA, ergine or LA-111; *Figure 1*) was first obtained as a semi-synthetic product by the degradation of ergotoxin by Smith and Timmis in 1932. In 1960, Hofmann and Tscherter isolated it as a genuine natural product from "ololiuqui", the seeds *Rivea corymbosa* (syn. *Turbina corymbosa*), the sacred narcotic-hallucinogen of the Aztecs. Since then LSA has been found in several ornamental morning glory (*Ipomoea*) species [56, 57]. The total ergot alkaloid content of the seeds of these plants is less than 0.2% with LSA and its 8-epimer (iso-LSA) being the most abundant.

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4. For further details, see: www.emcdda.europa.eu/publications/drug-profiles/salvia.
5. Information available from www.erowid.org/chemicals/salvinorin_b_ethoxymethyl_ether.

Table 1
Chronology of selected psychoactive natural products

Active principle	Original or common source(s)	Isolation	Structure[1]	Psychoactivity type[2]
Morphine	*Papaver somniferum*	1805	1925	narcotic-sedative
Caffeine	*Coffea arabica, Camellia sinensis, Cola nitida, Paullinia* spp.	1820	1882	stimulant
Nicotine	*Nicotiana tabacum, Duboisia* spp.	1828	1893	stimulant
Hyoscyamine	*Atropa, Brugmansia, Datura, Duboisia* spp.	1833	1897	hallucinogen/narcotic
Harmala alkaloids	*Peganum harmala, Banisteriopsis caapi*	1841-1885	1919	hallucinogen/sedative, monoamine oxidase inhibitor
Cocaine	*Erythroxylum coca, E. novogranatense*	1860	1898-1923	stimulant
Kavalactones[3]	*Piper methysticum*	1860-1959	1927-1959	anxiolytic/sedative
Ephedrine	*Ephedra equisetina (ma huang)* and other *Ephedra* spp.	1887	1889	stimulant
Bufotenine	*Bufo* toads; *Anadenanthera* trees	1893	1934	hallucinogen
Mescaline	*Lophophora williamsii, Echinopsis (Trichocereus)* spp.	1896	1919	hallucinogen
Ibogaine	*Tabernanthe iboga*	1901	1957	stimulant/hallucinogen
Mitragynine	*Mitragyna speciosa*	1921	1963-1964	stimulant/sedative
Psilocybin	*Psilocybe (Stropharia), Conocybe, Inocybe, Paneolus* spp.	1958	1958	hallucinogen
5-MeO-DMT	*Dictyoloma, Piptadenia* and *Mimosa* spp.; *Bufo alvarius*	1959	1959	hallucinogen
Lysergamide	*Rivea (Turbina) corymbosa, Argyreia nervosa, Ipomoea tricolor*	1960	1960	hallucinogen
Muscimol	*Amanita muscaria, A. pantherina*	1964	1964	hallucinogen
Δ[9]-THC	*Cannabis sativa*	1964	1964	sedative/hallucinogen
Ayahuasca[4]	*Banisteriopsis caapi* plus *Psychotria viridis*	--	1972	hallucinogen
Cathinone	*Catha edulis*	1975	1975	stimulant
Salvinorin A	*Salvia divinorum*	1982	1982, 1984	hallucinogen

[1]In some cases the structure was established independently by more than one research group.
[2]The type of activity may depend on dose.
[3]The first kavalactone to be identified was methysticin. Other 17 kavalactones, such as kavain and yangonin, were characterised subsequently.
[4]The main constituents of ayahuasca, *i.e.,* harmala alkaloids and DMT, had been known from other plants before their identification in the brew.

Ingestion of 50 to 100 seeds is needed to produce observable effects. Phytochemical screening of tropical climbing vines led to the discovery of LSA in the seeds of the Hawaiian baby woodrose (*Argyreia nervosa*) [58]. Interestingly, it is not the seeds but the leaves *A. nervosa* that are used in Ayurvedic medicine in India, where the plant is indigenous. The LSA-content of *A. nervosa* seeds shows high variability between batches and may reach 1% [59]. Five to ten seeds provide intoxication that lasts for 4-8 hours. Recent studies indicate that LSA and related alkaloids are not biosynthesized by the plant but produced by an associated fungus, which can be eliminated by fungicide treatment [60, 61]. Lysergamide and other alkaloid toxins are often present in endophyte-infected grasses and may cause poisoning in grazing animals [62].

Ergot alkaloids are "dirty drugs": they bind to several receptors thus eliciting a broad range of effects. However, neither the seeds, nor LSA induce classical hallucinations: rather, the (psycho)pharmacological effects are sedative-narcotic with feeling of complete emptiness [63]. The observed vegetative and psychotropic effects can be rationalized by the results of recent *in vitro* studies revealing that the

receptor profile of LSA is different from that of LSD [64]. The unpleasant effects of intoxication include salivation, nausea, diarrhea, tremor as well as psychosis, unpredictable behavior and even suicidal ideation [65-68].

Lysergamide is not listed in the UN Conventions, though it may be controlled either as a psychotropic substance or a precursor in some countries. The trade and sale of *Ipomoea* and *A. nervosa* seeds are largely uncontrolled.

Ayahuasca and its constituents

Ayahuasca or ayawaska ("vine of the souls"), also known as hoasca, caapi or yagé, is an ancient hallucinogenic decoction traditionally used in northern South America in ethnomedicine and, since the 1930s, as a sacrament by syncretic religious sects, such as the União do Vegetal or the Santo Daime in Brazil[6]. The key ingredients in the brew are the

6. Ayahuasca has been the subject of several scholarly edited books (see, *e.g.,* [69, 70]). The renewed global interest in ayahuasca, as made and used in South America, and ayahuasca-like preparations based on other plants indigenous to other continents, as well as the plethora of studies published recently on its use and effects justify a brief historical description as well as an update on studies not only of the brew but also its key ingredients.

pounded bark of the Amazonian woody liana *Banisteriopsis caapi* and the leaves of either the shrub *Psychotria viridis* or the vine *Diplopterys cabrerana*. The drink is usually made by mixing the two key components in boiling water. Admixtures, mostly solanaceous plants containing nicotine or tropane alkaloids, are occasionally added. Drinking the brew often induces vomiting, while the cardiovascular effects (bradycardia and reduced blood pressure) are only mild; mydriasis is typically observed. The psychotropic effects, accompanied by vivid visual imagery, usually last for 4-6 hours [71-73]. The side effects and relative safety of ayahuasca use have been reviewed [74, 75]. The physiological and psychological mechanisms of the promising anti-addiction effects of the brew offered in religious setting have recently been discussed [76].

The chemicals responsible for the dreamlike, colorful hallucinogen effects elicited by the brew were identified by Rivier and Lindgren in 1972: of the two plants, *B. caapi* is the source of harmala alkaloids, while *P. viridis* provides *N,N*-dimethyltryptamine (DMT) *(Figure 1)* [77, 78]. The first harmala alkaloid from the seeds of Syrian rue, *Peganum harmala*, was isolated by Goebel in 1841, while structural determinations were carried out by Manske *et al.* in 1927. These alkaloids, such as harmine, or 7-methoxy-1-methyl-9*H*-b-carboline *(Figure 1)*, and its di- or tetrahydro derivatives, are not particularly psychoactive on their own but, mainly in the gastrointestinal tract, inhibit monoamine oxidase (MAO) enzymes involved in the metabolism of monoamine neurotransmitters and certain xenobiotics [79, 80]. Passion flowers (*Passiflora* spp.) also contain harmala alkaloids but only in trace amounts; the pharmacological effects of preparations made from the plant are probably due to its flavonoid constituents [81, 82].

The primary hallucinogen component of ayahuasca is DMT, a low-melting point solid. The alkaloid was isolated from the seeds of *Piptadenia* (syn. *Anadenanthera*) species by Fish *et al.* in 1955 although it had already been synthesized by Manske two decades earlier. DMT, along with 5-methoxy-*N,N*-dimethyltryptamine (5-MeO-DMT), is also a psychoactive component of South American ceremonial snuffs prepared from *Anadenanthera*, *Mimosa* or *Virola* plants having various local names (cohoba, ebene, paricá, yopo, etc.) (see, *e.g.,* [83]). The psychoactivity and metabolism of DMT in humans were first studied by Szára in injection experiments in Hungary in the mid-1950s. Like all classical hallucinogens, DMT activates 5-HT_{2A} receptors *in vitro*. However, due to rapid inactivation by MAO enzymes, DMT is devoid of activity when taken orally explaining why the ritually or "recreationally" used DMT-preparations are administered either nasally or by inhalation to give hallucinations lasting for 15-20 minutes only. Ayahuasca is thus a unique, synergistic ethnobotanical drink in which the MAO-inhibitory action of harmala alkaloids enable the manifestation of the hallucinogen effects of the metabolically labile DMT.

There is no record on how or why these two particular plants were selected from the rich biodiversity of the Amazonian forest for the brew. The present author speculates that the ancient shamans initially experimented with a complex concoction made from several, perhaps dozens of plants. Having discovered activity of such a mixture, they could then proceed by using the leave-one-out technique, that is testing one by one a series of mixtures lacking just a single ingredient. This would then quickly reveal which

plants are indispensable for activity. Reconstituting a brew from the key components would then validate the procedure. It should also be pointed out that the brew contains other bioactive substances the contribution of which to the overall psychobiological activity has not been studied. The term "endohuasca" refers to human endogenous alkaloids chemically identical or similar to those present in the brew [84]; the actual (psycho)pharmacological role, if any, of such trace tryptamine metabolites is unknown [85]. The popular term "pharmahuasca" refers to the concomitant use of a synthetic MAO inhibitor with a tryptamine-type natural or synthetic hallucinogen [86].

Adopting practices of religious ayahuasca use, a number of follower groups have been established outside the Americas in recent years. While harmala alkaloids are regulated in a few countries only, DMT is an internationally scheduled psychotropic substance. In the USA, the sacramental use of "hoasca" falls under the "Religious Freedom Restoration Act" [87]. Nevertheless, the blooming "ayahuasca tourism" in Amazonia as well as the spread of ayahuasca and related preparations beyond traditional cultural boundaries have raised concerns and elicited debates on their regulation [88].

Bufotenine

Bufotenine, that is 5-hydroxy-*N,N*-dimethyltryptamine *(Figure 1)*, is an *N*-alkylated derivative of serotonin and also a structural isomer of the hallucinogenic psilocin, the 4-hydroxy counterpart. The chemical structure of bufotenine[7] was established by synthesis by Wieland *et al.* in 1934. Bufotenine and its ether derivative, 5-MeO-DMT, are the main ingredients of the psychoactive secretion of the American desert toad, *Bufo alvarius*. In fact, 5-MeO-DMT is one of the few psychoactive substances found in animals, and the hallucinogenic properties of this alkaloid is most likely behind the contemporary myth that "toad licking" elicits psychedelic effects [90]. The psychoactivity of bufotenine, however, is contested [85, 91]. Accompanying congeneric tryptamines, bufotenine also occurs in several hallucinogenic plants (see, *e.g.,* [92]). Interestingly, 5-MeO-DMT is oxidatively demethylated to bufotenine in the body [93]. The alkaloid binds to 5-HT_{2A} receptors *in vitro* with an affinity similar to that of DOB: the respective K_i values are 2.7 and 3.7 nM [7]. When taken orally, however, it lacks psychoactivity due to rapid inactivation by MAO enzymes [93-95]. Bufotenine is not listed in the UN Conventions yet it is controlled in a number of countries.

A related substance worth mentioning here is 5-methoxy-tryptamine, mexamine or 5-MeO-T. This endogenous trace amine is a serotonin receptor agonist and an enigmatic minor metabolite of the multifunctional neurohormone melatonin [96]. It has antioxidant and radioprotective effects in various biological systems but there is no information on its psychoactivity.

Ibogaine

The root of the tropical West African shrub *Tabernanthe iboga* is used in Gabon and Cameroon for its stimulatory and sedative-hallucinogenic properties. On one hand, the

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7. Bufotenine is an alkaloid and should not be confused with bufotoxins, or bufadienolides, which are cardiotonic steroids also present in toad skin and are the main bioactive ingredients of "Love Stone", an alleged aphrodisiac sold in some countries [89].

bitter roots of the plant, locally called iboga, are chewed to combat fatigue and to keep hunters awake. Based on such ethnopharmacological observations, a root extract (*Lambaréne®*) was available in France (1939-1966) as "neuromuscular stimulant". On the other hand, consumption of massive doses of iboga is part of the initiation ritual of the local Bwiti cult during which the initiate fells in deep coma that may last for a day. Of the structurally related alkaloids isolated from the plant the most important is ibogaine (12-methoxyibogamine) *(Figure 1)*, which is most abundant in the root bark (0.2-0.6%). The isolation of the light- and air-sensitive crystalline ibogaine was reported first in 1901, its structure was determined by Taylor in 1957. As with the root, ibogaine is stimulant at low (< 200 mg), while hallucinogenic at high (500-1000 mg) oral doses. The anti-addictive potential of ibogaine has received attention recently. In preclinical animal studies, acute ibogaine treatment reduced self-administration or symptoms of withdrawal of various addictive drugs, including ethanol, methamphetamine, nicotine and morphine. In humans, single or repeated oral doses of 4-25 mg/kg have been shown to alleviate withdrawal symptoms and craving, confirming anecdotal reports and patent claims originating from the 1960s [97-99]. However, due to serious adverse side effects, such as tremor, ataxia, cardiac toxicity and even fatalities, NIDA-coordinated human clinical trials were halted in 1995 [100-102]. According to recent studies, the alkaloid, at therapeutic concentrations, disrupts the heart's electrophysiology that could lead to life-threatening cardiac arrhythmias [103, 104]. In rodent models of ethanol-addiction, certain synthetic analogues have improved toxicological profile and appear to be as effective as the natural alkaloid [105]. Ibogaine and its demethylated metabolite, namely 12-noribogaine (12-hydroxyibogamine) (see, *e.g.*, [106]), have complex pharmacology affecting several neurotransmitter and transporter systems [99, 107, 108]. The glial cell line-derived neutrophic factor, which is necessary for the proper functioning of dopaminergic neurons, appears to be also involved in the sustained anti-addictive effects of the alkaloid [109]. In the mouse, ibogaine was more toxic than 12-noribogaine (the respective intragastric LD_{50} values are 263 and 630 mg/kg) [110]. In spite of the health risks, controversial "ibogaine anti-addiction therapies" continue in private clinics and non-clinical setting in some countries where the substance is not regulated. Ibogaine is seldom used recreationally.

Kratom

Kratom (*Mitragyna speciosa*)[8], or "krathom" (Thailand) and "biak" or "ketum" (Malaysia), is a tropical tree indigenous to South East Asia, the Philippines and New Guinea. Traditionally, the chopped fresh or dried leaves of the tree are chewed or made into tea. Kratom preparations have been used in local medicine, and also as stimulants or an opium substitute. Of the over 40 structurally related alkaloids isolated from various parts of the tree the most abundant (up to 2% in the leaves and leaf preparations) is mitragynine (9-methoxycorynantheidine) *(Figure 1)* [111-113]. The alkaloid was isolated first by Field in 1921, its chemical structure was clarified by Joshi and Zacharias in 1963-1964. A minor though pharmacologically important alkaloid, namely 7-hydroxymitragynine, was discovered in

the leaves by Ponglux *et al.* in 1994. There are few human clinical studies with kratom or its alkaloid constituents [114-116]. At a low dose, leaf preparations act as "cocaine-like" stimulants and are traditionally used to combat fatigue during work. At high dosages (10-25 g of dried leaves), however, "morphine-like" sedative-narcotic effects manifest: the initially occurring sweating, dizziness, nausea and dysphoria are superseded with calmness, euphoria and a dreamlike state lasting for several hours. Contracted pupils (miosis) are also noted. Regular kratom use may cause constipation, anorexia and hyperpigmentation of the cheek; dependence may develop [117]. Withdrawal symptoms are relatively mild and typically diminish within a week [118].

The narcotic and antinociceptive effects of kratom are attributed to mitragynine and 7-hydroxymitragynine acting as µ-opioid receptor agonists [113]. In this respect, 7-hydroxymitragynine is several times more active than morphine both *in vitro* and *in vivo*. Recent studies revealed the roles of κ -opioid and dopamine D1 receptors in the various effects of kratom [119]. The serotonergic and adrenergic systems are also involved in the psychological and physiological effects of mitragynine. The pharmacological mechanisms responsible for stimulant activity are yet to be established.

According to animal studies, kratom is only slightly toxic [120]. In rats, for example, oral administration of a kratom leaf-extract (1.6% mitragynine content) at 1000 mg/kg caused transient toxicity (slow movement and rapid breathing) but no mortality, while morphine had depressant activity with 25% mortality at 430 mg/kg; oral mitragynine doses as high as 806 mg/kg were not lethal. Intravenous injection of mitragynine at 9.2 mg/kg to rhesus monkeys produced only transient toxic symptoms. In mice, repeated 7-hydroxymitragynine administrations elicit tolerance, cross-tolerance to morphine, and naloxone-precipitated withdrawal symptoms [121]. There have been few poisoning cases related to kratom consumption [122-124].

In Asia, local shops may sell fresh kratom leaves in bundles, while in foreign countries crushed or powdered dried leaves are available. Herbal products fortified with kratom leaf extracts are also marketed worldwide. It is of note that fatal intoxications involving fake kratom preparations adulterated with O-desmethyltramadol, a bioactive metabolite of the synthetic opioid analgesic tramadol, have recently been reported [125]. Fentanyl-laced kratom-preparations have also been seized in the USA [126].

Although still uncommon – and mostly unregulated – outside Asia, kratom has become one of the most widely abused illicit substances in Malaysia and Thailand either as a drug by itself or a substitute for opium or alcohol [117, 127, 128].

Kava

Kava, awa, yaqona or "intoxicating pepper" (*Piper methysticum*) is a large-leaved shrub indigenous to the South Pacific Islands. It is also the name of the mildly narcotic beverage made by extracting the rootstocks of the plant by water at ambient temperature. On many of the Islands, kava drinking is an integral part of social life. The plant was probably first domesticated in Vanuatu and, by now, it has spread throughout the region. The many different cultivars (or chemotypes) grown on the Islands today have been selected over generations; the clones are propagated vegetatively. Kava products, either the dried and powdered roots

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8. For further details, see: www.emcdda.europa.eu/publications/drug-profiles/kratom.

or root organic solvent extracts, are important agricultural commodities in that region with annual export values exceeding US$ 11 million [129]. Kava preparations have also been used in traditional medicine to cure fever, pain, headache, respiratory problems, insomnia, diarrhea or constipation, skin diseases, convulsion, urogenital and menstrual problems. In the early twentieth century, kava products were sold in Europe for the treatment of various illnesses [130]. The effects of the drink include mild euphoria and sociability, as well as anesthesia and astringency in the tongue and the inner lining of the mouth. Small doses typically produce stimulation while larger ones cause muscle relaxation, incoordination, and somnolescence. Regular and heavy use of kava, either the drink or the extracts, is not without risks: transient dermopathy (dry scaling skin), liver and kidney problems, gastrointestinal distress, as well as impaired vision have been observed [131, 132].

Since the initial studies on the separation of the individual kava-constituents by Cuzent around 1860 and by Lewin in the mid-1880s, the phytochemistry of *P. methysticum,* has been fully explored [133, 134]. The psychoactive principles of the roots are the so-called kavalactones (kavapyrones), exemplified by kavain (also spelled kawain) and yangonin *(Figure 1)*. The total kavalactone content may vary from 3 to 20% of the dried root. The composition of the aqueous beverage and the organic extracts mainly depends on the type of the cultivar though environmental factors and the extraction method employed also affect the kavalactone content [135, 136].

The mode of action of kava in the central and peripheral nervous system is complex and not fully understood. Each kavalactone has a distinct pharmacological profile involving GABA and benzodiazepine receptor sites, voltage-gated cation channels, monoamine reuptake and metabolism, the arachidonate cascade, and the endocannabinoid system [131, 137]. Accordingly, there can be substantial variations in the effects between various chemotypes; drinkers are said to prefer cultivars with high kavain content [136]. It must also be noted that constituents other than the kavalactones may play a role in the various pharmacological or pathophysiological effects of the aqueous extract though this issue has received scant attention (see, *e.g.*, [138, 139]).

In recent decades, kava root extracts, formulated as capsules or tinctures, became available worldwide as dietary supplements and clinically proven over-the-counter medicines for anxiety, depression and insomnia [131, 140]. Since 2002, however, several European countries restricted the sale of such extracts due to reports about hepatotoxicity of still unresolved etiology [141-143]. Nonetheless, dried and finely ground roots, having a light greyish-brown color resembling sawdust, are offered in herbal shops and on the Internet. Because of the economic importance on one hand and of the uncertainties of the health risk associated with kava products on the other, the developments of regional and FAO-WHO Codex Alimentarius standards for kava have been recommended[9]. A few countries have, in recent years, regulated kava as a psychotropic drug.

Betel

After caffeine-containing beverages and tobacco, betel is the third most widely used stimulant: it is chewed regularly by at least 400 million people throughout east Africa, Asia and the Pacific Islands as well as migrant communities therefrom [144-147][10]. Betel or, more accurately, a betel quid is made of three essential ingredients: slices of nuts of the areca palm (*Areca catechu*), spread with slaked lime and wrapped in the heart-shaped leaf of the betel palm (*Piper betle*). Tobacco may be a common ingredient and spices, such as aniseed, cardamom, cloves, coconut, ginger, nutmeg or sugar, are frequent flavoring additives. In India, the sale of tobacco-containing betel products known as "gutka" was restricted in 2011. Freshly prepared quids are usually sold by street vendors or, in Taiwan, by "betel nut beauties" along busy roads. The quids are placed between the cheek and the tongue, pressed against the teeth to remove the juice, which is then swallowed. Due to the coloring ingredients of the nuts, the reddish spittle stains the chewer's gums and lips (as well as the roadside…). Industrially manufactured, tobacco-free areca products called "pan masala" are sold in convenient sachets. Fresh or dried nuts, called "supari" in India, cut into small pieces may also be masticated alone. Areca and betel preparations have been used in traditional, for example Ayurvedic, medicine for centuries. Areca nut is a commodity in Asia with about 650 000 tonnes produced annually [149]. Bulk quantities of synthetic arecoline salts have also appeared recently in on the Internet for sale.

The alkaloid constituents of areca nut were structurally characterized by Jahns in 1888-1891. The principal alkaloid is arecoline, namely the methyl ester of 1-methyl-1,2,5,6-tetrahydropyridine-3-carboxylic acid *(Figure 1)*, a nicotinic acid derivative. The arecoline content of the nuts may reach 1%. Arecoline, a colorless liquid, can readily be synthesized and its salts are deworming (purgative) agents used in veterinary medicine. There are three other related alkaloids present in the nut: arecaidine, which is the free carboxylic acid derivative of arecoline formed also during mastication and ingestion; guvacine, which is the *N*-desmethyl derivative of arecaidine; and guvacoline, which is the *N*-desmethyl derivative of arecoline.

The leaves of the betel palm contain phenylpropanoids, such as chavibetol *(Figure 1)*, eugenol and safrole, as well as terpenes but the contribution of these aroma constituents to the psychoactivity of the quid is not known.

In spite of widespread use, the physiological and psychological profile of betel quid intoxication is just beginning to be delineated [150]. More is known about the pharmacology and toxicology of its alkaloidal constituents [151]. The active ingredients, absorbed into the blood via the mucous membranes of the mouth and the intestine, affect both the central and peripheral nervous systems. Betel, due to its predominant alkaloid, arecoline, which is a known muscarinic acetylcholine receptor agonist, elicits mostly cholinergic (parasympathomimetic) symptoms and elevated adrenaline plasma concentrations. The minor alkaloids are GABA uptake inhibitors and presumably modulate the psychoactivity of the quid.

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9. See: http://acp-mts-programme.org/en/contents/pacific-high-level-meeting-on-kava-12-15-march-2012 and ftp://ftp.fao.org/codex/meetings/CCNASWP/CCNASWP12/na12_08e.pdf.

10. For the historical and cultural aspects of as well as artistic utensils associated with betel chewing, see the lavishly illustrated book by Rooney [148].

The typical psychological effects are mild and include relaxation, light euphoria and improved concentration. Somatic symptoms include miosis, intense salivation, facial flushing, sweating, palpitation, bronchoconstriction (risk of asthma!), and increased gastrointestinal motility, though chronic users develop tolerance to many of these effects. Novice users or regular chewers ingesting large amounts may experience tremor, dizziness, diarrhoea, vomiting and acute psychosis.

Excessive use of areca nut and betel quid has been associated with a number of health-related problems: discoloration of teeth and gums, sometimes turning reddish-brown, mouth ulcers and gum disease, oral submucous fibrosis and oral cancers, including squamous cell carcinoma, peptic ulceration, increased risk of cardiovascular disease. The major concern of betel chewing is the risk for the development of oral cancer associated with its alkaloid ingredients and, in particular, their nitroso and *N*-oxide derivatives [152,153]. The risk of malignant oral disorders increases when tobacco is included in the quid [154]. Recently, however, *Rai et al.* [155] have proposed that some non-alkaloidal phytochemicals (polyphenols and terpenoids) present in betel palm leaves may, by various mechanisms, counteract the carcinogenic effects of areca and tobacco alkaloids. Due to its cholinergic effects, arecoline may clinically improve the cognitive performance of Alzheimer's patients [156]. Dependence and withdrawal symptoms have been noted [157]. Few countries regulate the palm or its alkaloids.

LESSER-KNOWN PSYCHOACTIVE NATURAL PRODUCTS
Glaucine
The alkaloid glaucine, also known as boldine dimethyl ether or 1,2,9,10-tetramethoxyaporphine *(Figure 1)*, is found in the yellow horned poppy (*Glaucium flavum*, formerly *G. luteum*), indigenous to the Mediterranean region, as well as in other plants, such as *Croton lechleri* (source of the latex "sangre de grado") or the Chinese medicinal plant *Corydalis yanhusuo*. The alkaloid was isolated by Fischer in 1901, its structure determined by Gadamer in 1911. Glaucine can also be synthesized either from the readily available boldine or, in racemic form, from papaverine. The therapeutic value of glaucine is similar to that of codeine or dextromethorphan [158, 159] but with lower abuse potential [160]. The plant has been used in folk medicine while glaucine itself is registered in some East European countries as an over-the-counter, non-opioid antitussive and bronchodilatory medicine. The alkaloid was shown to be an effective blocker of calcium ion channels of bronchial smooth muscles, as a week antagonist of dopamine receptors, as an antagonist of peripheral serotonin receptors, as a non-selective α-adrenoreceptor antagonist, as a selective inhibitor of phosphodiesterase type 4 isoenzyme, as an antioxidant and a resensitizer of multidrug resistance of cancer cells (see, for example, [161]). Glaucine has been reported to cause weakness, sleepiness, nausea, mydriasis and visual or dissociative-hallucinations both with therapeutic and recreational use but the underlying pharmacology responsible for these central effects remains to be determined [162, 163]. Glaucine-containing tablets and herbal mixtures have appeared recently as "herbal highs" in the several European countries [162, 164, 165].

Pituri
Pituri, pitchery or chewing tobacco (*Duboisia hopwoodii*), is a solanaceous shrub growing in the arid region of Australia. Its dried and powdered leaves, often mixed with ash obtained from the burning of some other plant, are made into a quid, which is then chewed by Aboriginal groups to alleviate fatigue, hunger and pain; plant preparations are also used to kill game and fish [166]. The identity of one of the alkaloids in the leaves was unequivocally confirmed in 1911 by Rothera as the cholinergic nicotine *(Figure 1)*. The roots of *D. hopwoodii* are, however, particularly rich in anticholinergic tropane alkaloids, *e.g.*, hyoscyamine, also called duboisine or daturine *(Figure 1)*, and its 6,7-epoxide, scopolamine. Related alkaloids have also been isolated from the leaves and roots of other Australian *Duboisia* (corkwood) species since the 1870s [167], and are of ethnopharmacological interest. Such deliriant tropanes are the principal bioactive alkaloids of many solanaceous plants, including the legendary *Atropa* (belladonna), *Brugmansia* (angel's trumpet), *Datura* (jimsonweed, thornapple), *Mandragora* (mandrake) and *Solandra* (chalice vines) species. Some *Solandra* species called "cup of gold" are woody, tree-like climbers indigenous to Mexico and tropical America and were once used by the Aztecs as sacred hallucinogen ("tecomaxochitl"); the plants are still revered in Mexico by Huichol Indians who call them "kiéri" [168]. Hyoscyamine is used in medicine in some countries, for example in antiulcer therapy, while scopolamine and its derivatives are employed in veterinary and human medicine; for example, transdermal scopolamine formulations, to prevent nausea and motion sickness [169]. The not uncommon abuse of *Datura* species to induce hallucinations is often associated with severe complications, although these are rarely fatal (see, *e.g.*, [170, 171]). Pure scopolamine or *Datura* and *Brugmansia* preparations ("burundanga"; popularized as Devil's breath) cause transient amnesia and their use to incapacitate crime victims, especially in Colombia, is well documented [172, 173].

Wild lettuce
Wild lettuce, bitter lettuce or lettuce opium (*Lactuca virosa*), wildly growing in Eurasia and Northern Africa, is a tall (up to 150 cm high), poisonous and skin irritating relative of the garden lettuce (*L. sativa*). The analgesic, sedating, hypnotic and cough-suppressing properties of its seed extracts and of the milky latex (lactucarium), released from its stem and leaves upon wounding, have been known for millennia [2, 174][11]. Lactucarium is obtained from *L. virosa* or *L. sativa* and used like opium in traditional medicine and various preparations form these species were listed in pharmacopoeias of several countries up to the early twentieth century. The smoked dried leaves of the plant can also serve as marijuana substitute. In spite of the long history of its use, not much is known about the pharmacology of *L. virosa* and of its chemical constituents. The latex contains bitter sesquiterpene lactones thought to be responsible for the characteristic pharmacological properties of the plant [176]. One of the most studied sesquiterpene is lactucin *(Figure 1)*, which is present either in free or esterified form

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11. The sesquiterpene lactones present in the latex have ecological importance: these bitter and chemically reactive substances are part of the defense mechanism against predators (for a recent review covering human health related adverse effects, see [175]).

also in other lettuce species as well as in chicory. Crystalline lactucin was isolated in pure form by Schenk and Graf in 1936 and its bicyclic lactone structure, related to that of the bitter principle of absinthe, was established independently in the laboratories of Barton and of Šorm in 1958. Apart from the (user-)reported narcotic-euphoric effects resulting form recreational use, there is scant contemporary information on the (psycho)-pharmacological properties of either the latex or its pure ingredients [174]. The sedative and analgesic activities of lactucin were confirmed in mice though opioid receptors were unaffected *in vitro* [177, 178]. The symptoms observed in human wild lettuce-poisoning cases differ from those of traditional opiates [179, 180]. The precise molecular targets of the latex and its constituents are yet to be established. Wild lettuce preparations, including fortified extracts, are freely offered on many Internet sites and by herbal (smart) shops.

Kanna

Kanna, channa or sceletium (*Mesembryanthemum* - formerly *Sceletium* - *tortuosum*) is a creeping perennial plant with succulent leaves. It is indigenous to southern Africa where it has traditionally been used (mainly chewed as quid) by the Khoe-San people to elevate mood, relieve hunger and thirst. The psychoactivity of this relatively little studied plant and its "fermentation" product ("kougoed" in Afrikaans) is attributed to a structurally related group of alkaloids of which the most abundant is mesembrine *(Figure 1)*. Mesembrine was isolated by Zwicky in 1914 and its structure identified in 1960 (see [181, 182]). Laboratory experiments with various plant preparations have revealed anti-stress, antidepressant, narcotic, anxiolytic and anti-addictive but not hallucinogenic effects [182, 183]. Screening *in vitro* a range of potential pharmacological targets revealed that mesembrine was an effective inhibitor of 5-HT reuptake, while its unsaturated derivative (*i.e.*, mesembrenone) inhibited both 5-HT reuptake and phosphodiesterase type 4 isoenzyme [184, 185]. These results, at least partly, support the observed psychoactive properties of the plant.

Many Internet sites and herbal shops offer powdery kanna preparations, including fortified extracts, that vary in their mesembrine-type alkaloid-content and, consequently, in their psychoactivity [186]. In 2013, a standardized extract (Zembrin®) became available as a mood-enhancer and anxiolytic botanical supplement [185].

OBSCURE OR FALSE "NATURAL" PSYCHOACTIVE SUBSTANCES

There has been a resurgence of interest in natural products in general, and suppliers of dietary supplement and unregulated psychoactive substances try to profit from it. In recent years, however, chemical scrutiny have revealed that some herbal mixtures advertised as "natural" or "herbal high" contain undisclosed synthetic additives as bioactive constituents. Fake kratom products adulterated with synthetic opioids have already been mentioned. A most dramatic development was the appearance on the drug market, in around 2004, of smokable herbal mixtures under the brand name "Spice", mimicking the effect of marijuana [187]. Since then, the number of herbal preparations laced with structurally diverse synthetic cannabinoid receptor agonists, originally invented by academic or industrial research laboratories, has been growing incessantly [188-190]. There have been, however, other cases for which the origin of psychoactive ingredients in the natural products was or still is enigmatic. A few selected but representative examples are mentioned below.

Clement *et al.* [191] reported the detection of psychoactive phenethylamines, including mescaline as well as amphetamine and *p*-methoxyamphetamine, in *Acacia* species growing in southwest Texas and northern Mexico. No other analyses have substantiated these intriguing findings. Since drugs have been found to be ubiquitous in our environment, including air (see, *e.g.*, [192]), it is suspected that the isolated compounds, the amphetamines in particular, were artifacts due atmospheric transport from the site of their production or use. A similar case concerns the sub-Saharan *Nauclea latifolia* (or *N. esculentus*), commonly known as pin cushion tree, African peach or Guinea peach, which has been used in local ethnomedicine for the treatment various ailments. Recently, the synthetic opioid analgesic tramadol has been isolated from the root bark of the plant [193]. Although the structure of the compound was unequivocally proven by multiple analytical methods, the true origin of this substance with a structure unprecedented in nature remains to be established. In the author's opinion these two cases are most likely further examples of the so-called "semi-natural products", defined recently as man-made substances that are (re)isolated from natural sources [194].

Another widely occurring natural phenethylamine is also worth mentioning here. Hordenine or *N,N*-dimethyltyramine (*p*-hydroxy-*N,N*-dimethylphenethylamine; also known as anhaline) is a minor alkaloid not only of peyotl (*Lophophora williamsii*) and other cacti, but *Acacia*, *Sceletium* and *Phalaris* plants [195]. Since germinating barley (*Hordeum* spp.) produces hordenine, the alkaloid is present in beer [196] and is readily identifiable in the urine of beer drinkers. Thus, its presence in urine should not be considered an indicator of synthetic drug use, as proposed [197], but rather as an indicator of beer consumption [198]. The human psychoactivity of hordenine is not known. It is of note, however, that this phenolic alkaloid could cause false positives in morphine immunoassays of beer drinkers' urine [199].

The final case concerns a stimulant substance, namely 1,3-dimethylamylamine or DMAA in short (systematic name is 4-methylhexan-2-amine; four stereoisomers exist) *(Figure 1)*. It is often advertised as "geranamine" alluding to an obscure report on its detection in geranium essential oil (see: [200]). Recent studies, unable to identify this volatile amine in commercial geranium oil samples and food supplements, refuted the claims that "geranamine" is natural product [201-203]. In fact, DMAA is one of the branched aliphatic amines synthesized by pharmaceutical companies in search for novel amphetamine analogues [204]. It was marketed as a nasal decongestant (*Forthran*®) until the 1970s. The mild stimulant effect of DMAA is comparable to caffeine [205], but its use is not without health risk [206]. Though a prohibited doping agent, DMAA is a frequent ingredient of dietary supplements sold for athletes. Immunoassays developed for amphetamine-type drugs may show cross-reactivity with DMAA [207].

CONCLUSIONS

Tourism, migration, international trade as well as the boundless flow of information via the Internet all contribute to the global spread of many once exotic psychoactive drugs [208, 209]. Between January 2005 and December 2012, some 230 new psychoactive substances have been

reported to the EWS of EMCDDA but only less than twenty of these can be considered as natural products. For practical reasons, many of them (*e.g.*, bufotenine, harmaline, 5-MeO-DMT, phenethylamine) are certainly obtained by synthesis rather than isolated from a natural source. Acknowledging that the numbers reported by the EMCDDA indicate only the mere presence (actually the detection) of a substance and not the amount of sales or the extent of use, it appears that the new drugs market is now dominated by synthetic substances. Apparently, the importance of natural products and the role of traditional ethnopharmacological research, oriented mainly towards plants, have diminished over the past two decades. In spite of extensive screening campaigns (*e.g.*, [210-213]), hardly any novel natural psychoactive substance has been discovered since the identification of salvinorin A in 1982. Could the natural sources of new drugs be exhausted? Although there are dozens of exotic herbal drugs that are sold and used for their proven or alleged "psychoactivity", neither their psychopharmacology nor their key ingredients have been characterized and

it is unlikely that they contain hitherto unknown but potent ingredients. Perhaps marine organisms, a largely untapped source of psychoactive compounds, will provide novel substances with interesting structure and activity [214, 215]. One thing is certain, however: the molecular scaffolds created and used by Nature will continue to serve as key design elements in future generations of (semi-)synthetic substances that could become valuable research tools or even therapeutic agents. It also seems to be inevitable that some of such potent synthetic analogues will be diverted into the recreational scene.

Conflict of interest statement

There are no potential conflicts of interest or any financial or personal relationships with other people or organizations that could inappropriately bias conduct and findings of this study.

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