CHAPTER

14

Natural Product (Fungal and Herbal) Novel Psychoactive Substances

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INTRODUCTION

Natural product drugs of abuse are as old as mankind with *Cannabis* (*Cannabis sativa*), Opium (from *Papaver somniferum*) and cocaine (from *Erythroxylon coca*) being ancient examples of materials which were used in pain relief or in religious ceremonies [1]. Natural product novel psychoactive substances (NPS) ('legal highs') are legally-available products from natural sources including plant or fungal materials that may be either extracts or crude plant or fungal material that contain compounds that elicit a psychoactive effect. This is distinct to the synthetic chemicals (single chemical entities; SCE) covered in the other chapters of Section 3 of this book. Both the natural product and the single chemical NPS are used as substitutes for and/or in addition to establish, classical recreational drugs such as cocaine, amphetamines, hallucinogenic materials related to tryptamine and analgesic drugs of the opiate class.

An important United Kingdom (UK)-based Internet market survey undertaken in 2011 [2] showed that 1308 kinds of product were available with an average price of £9.69. Most of these materials were in the form of pills (46.6%) while 18.1% were single plant materials or plant extracts. The top five plant-related products by frequency were *Salvia* (*Salvia divinorum*), kratom (*Mitragyna speciosa*), Hawaiian baby woodrose seeds (*Argyreia nervosa*), fly agaric (*Amanita muscaria*) and 'Genie' (a smoking mixture containing multiple plant materials and of dubious pharmacognostical identity).

This chapter will focus on the NPS that are natural products, namely extracts of plants or the crude fungal or herbal materials themselves. The term 'legal' will be applied to the UK at the time of writing this chapter as legality varies from country to country and is time dependent as more is understood about the harms associated with these materials and individual countries consider classification of these substances.

NPS products are widely available and easily affordable from the Internet and retailers. This ready availability has resulted in an expansion of use and increasing sales of these materials in Europe and globally. According to the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) Report in 2011, the number of online sites selling NPS in July 2011 was found to be two- and three-fold greater

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than in the last six and 18 months, respectively. A third of 631 online shops found in the study were based in the USA, while a fifth were in the UK [3]. This is cause for considerable concern and some countries, such as the USA, have seen an increase in the use of hallucinogenic substances over the past decade [4]. This increasing use coupled with a steady stream of case reports of adverse effects from NPS products shows that this area will be of societal importance for some considerable time to come [5].

Many of the natural product NPS currently in use were studied for their chemistry some time ago, and it should be noted that there is still a requirement for modern analysis of some of these complex natural materials. The paucity of data casts further doubt on the acute safety of these products and their long-term safety profile. Further natural product chemistry is needed on the analysis of the minor chemical components, their pharmacology at various receptor types, their biological activity as a mixture and their interactions with existing controlled drugs of abuse, and even their interactions with conventional medicines needs further study. This chapter will cover the main fungal and herbal NPS and give an overview of their chemistry, pharmacological action where known and recent toxicological reports.

FUNGAL NPS

Fly Agaric (*Amanita Muscaria*)

Amanita muscaria is a member of the Basidiomycete group of fungi [6] and is the classic toadstool depicted in literature and art with a red or orange cap that is often mottled with white spots. When dry these specimens have an orange/brown colour but the mottled spotting is still clearly visible (Fig. 14.1) and NPS samples are sold as bagged-up whole basidia (caps).

Figure 14.2 shows a NPS product purchased on the Internet and disingenuously labelled 'not for consumption', despite there being no rational reason other than for research purposes for possession of this material.

Within this genus there are a number of poisonous relatives including the panther (*Amanita pantherina*), the death cap (*Amanita phalloides*)

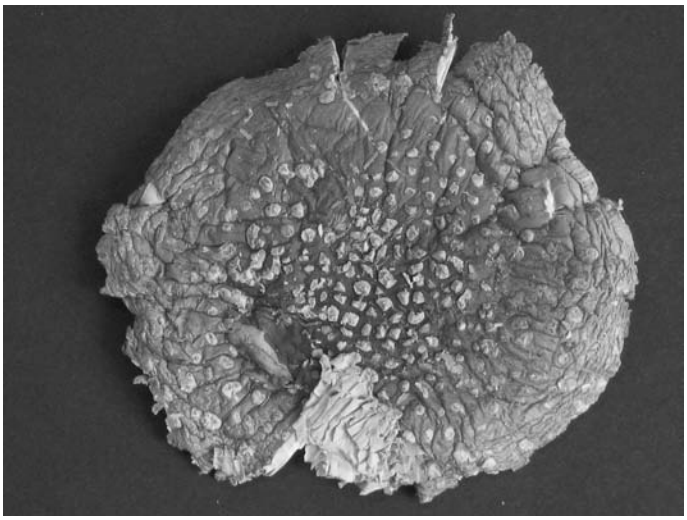


FIGURE 14.1 Cap of *Amanita muscaria* showing the distinctive mottled spots characteristic of this species.

and the delightfully termed destroying angel (*Amanita verna*) [6].

Fly agaric has a long history of use as a sedative material and the main psychoactive compounds within these species are thought to be analogues of the neurotransmitter gamma-aminobutyric acid (GABA) and glutamic acid, notably muscimol and ibotenic acid, respectively [7] (Fig. 14.3).

The natural products muscimol and ibotenic acid are isoxazole alkaloids and possess some structural similarity with GABA and both act at various parts of the GABA receptor. Muscimol is derived from ibotenic acid by decarboxylation [8]. Muscarine is a cholinergic agonist and was thought to contribute to the overall psychoactivity of *A. muscaria*. However, it was reported later that the mushroom contained only trace amount of muscarine so it is unlikely to be responsible for the psychoactive effect [9].

The use of this material is steeped in history and it has been suggested that fly agaric is Soma, the vedic drug consumed by the Indo-Iranians. Poisoning by this species has been described as the '*pantherina–muscaria*' syndrome and is 'atropine like' and comparatively rare. Symptoms can manifest between 30 minutes and two hours and include dizziness, confusion, tiredness, and increased sensitivity to visual and auditory stimuli. The 'atropine-like' effects also include dryness of mouth, pupil dilation and followed by drowsiness with a deep sleep [10,11]. Effects have been compared to alcohol consumption but with hallucinations, incoherent speech, possible seizures, vomiting, transient deep sleep or coma and persistent headache [4]. Treatment of toxicity associated with *A. muscarina* includes gut decontamination and in severe cases the use of benzodiazepines; some authors have suggested that the use of a cholinesterase inhibitor such as

FIGURE 14.2 A legal high purchase of *Amanita muscaria* (Fly Agaric) 'labelled not for consumption'.

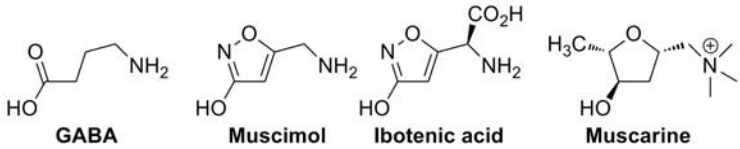


FIGURE 14.3 Structures of Gamma amino butyric acid (GABA), muscimol, ibotenic acid, and muscarine.

physostigmine may need to be considered [12]. In some countries fly agaric is consumed as food stuff but the red skin is removed and the mushroom is soaked or boiled and the resulting water is discarded, and this would presumably have an effect on reducing the concentrations of the isoxazoles, and therefore reduce the risk of psychotropic effects. A few case studies have been reported with one example of a 48- year-old male having consumed fly agaric, vomited and fell asleep 30 minutes after consumption, being found later comatose and having a seizure-like episode. Four hours after admission he was still comatose and was administered activated charcoal and awoke 10 hours after ingestion. At 18 hours his condition deteriorated with paranoid psychosis and visual and auditory hallucinations which persisted for five days. This case report suggested that a delay can occur with the onset of poisoning and that psychosis may last several days [13].

One case report has shown respiratory and cardiovascular depression with ingestion of fly agaric with myoclonus, flushing and mydriasis and treatment included the use of intravenous atropine, diazepam and mechanical/assisted ventilation [14].

Psilocybe and Related Species – 'Magic Mushrooms'

Magic mushrooms of the genus *Psilocybe* are still marketed as 'novel psychoactive substances', notably the spores and mycelia of *Psilocybe cubensis* and *Psilocybe semilanceata*, which are sold with sand as 'specimens for microscopy'. The addition of water allows fruiting of the mushrooms after a few days. Sometimes spores are sold as a suspension in solution in a sterile syringe and when this suspension is added with water to a suitable fruiting matrix, for example a breakfast cereal, the spores will germinate and produce fruiting bodies (the mushroom caps; basidia) [15].

Possession of the whole fresh or dried prepared material of *Psilocybe* is an offence in the UK and 'head shops' and websites circumvent this legislation by marketing the spores in suspension as an aid to microscopy and a microbiological training aid. The main psychoactive components are, however, Class A drugs in the UK.

Specifically, these species contain the phosphate ester psilocybin which is hydrolyzed *in vivo* to psilocin, which is the main psychoactive component of magic mushrooms and shows marked similarity with serotonin (Fig.14.4). Psilocybin is a serotonin agonist and has high affinity for the $5HT_{2A}$ receptors [4].

The symptoms of psilocybin and psilocin intoxication are similar to that of LSD and mescaline, but with a shorter action [16]. The acute toxicity of aqueous extracts of *P. cubensis* has been investigated in rats with an increased rearing behaviour, gnawing and even a gender difference being observed [17]. Psilocybin-like myocardial toxicity has also been investigated [18] and the authors concluded that sub-chronic intoxication may lead to a magnesium imbalance without affecting the concentrations of calcium, sodium, potassium or chloride.

FIGURE 14.4 The structures of the main components of *Psilocybe*, psilocybin and psilocin, show marked similarity with serotonin.

In the 1960s and 1970s collections of the Liberty Cap (*Psilocybe semilanceata*) across various parts of the UK was a popular endeavour; users reported vivid visual hallucinations and auditory disturbances [19]. Case reports for the sensory hallucinogenic effects of magic mushrooms are manifold [20,21] and whilst significant systemic toxicity appears to be rare, the main cause of fatality arises from misadventure due to psychosis [22]. In a Swedish study looking at intoxications by analysis of urine content over a 4-year period covering 103 cases, psilocin was found to be the most frequently observed psychoactive and was found in 54% of cases [23].

An example of this includes resisting arrest and the assault on a police officer [24] where the assailant was intoxicated with psilocin after ingesting 4 mg of magic mushrooms and attempts to subdue the assailant with nine bean bag rounds and multiple Taser usage failed. The man subsequently was shot trying to enter a police car containing a loaded rifle. Analysis of a post-mortem urine sample reported 4200 ng/mL of psilocin. This case demonstrates the psychotic, bizarre and 'seemingly purposeful behavior' [24] that these materials can elicit. However, an important and recent review by Van Amsterdam and co-workers [25] on *Psilocybe* use in the Netherlands has concluded that its use is relatively safe and that only a few and mild adverse effects have been reported. According to the Coordination point Assessment and Monitoring new drugs (CAM), Netherlands, the dependence potential of the mushroom was low as well as chronic toxicity while acute toxicity was moderate. However, the unpredictable nature of panic attacks and flashbacks associated with this material remain a point of concern.

Herbal NPS

Catha edulis (Khat)

Khat (*Catha edulis* Forsk. ex Endl.) is a small tree from the Celastraceae plant family that grows in East Africa and the Southern Arabian Peninsula. The crude drug material has a number of names in various locations such as 'qat' (Yemen), 'tchat' (Ethiopia), 'qaad or jaad' (Somalia) or 'miraa' (Kenya) [26]. The chewing of khat is part of the ethnic culture of Yemeni, Somali and East African societies especially at social gatherings. The fresh leaves of this species are consumed every day by approximately 80–90% of men and 10–60% of the women in East Africa [27], primarily due to its central nervous system (CNS) stimulating and euphoric effects [28].

Khat use has spread with immigration to other parts of the world, such as Europe and America, by East Africans. Users ingest approximately 100–500 g of leaves or stem bark by chewing every one or two hours to ingest the juice. Chewing is the most common form of using khat; other routes of use include drinking as a tea, smoking or nasal insufflation, although these routes are far less common [29,30]. Various natural products of the alkaloid, flavonoid, terpenoid, tannin, and glycoside classes have been characterised but it is the alkaloids of the phenylethylamine group that are the main pharmacological principles [28,29,31]. *S*-cathinone (Fig. 14.5), the

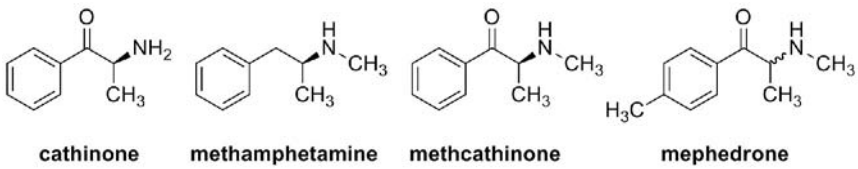


FIGURE 14.5 Structure of cathinone and its relationship with methamphetamine, methcathinone and mephedrone.

main phenylethylamine alkaloid is found to be present at around 78–343 mg/100 g of fresh khat leaves [28,32], and is currently thought to be the major active component responsible for the pharmacological effects [29,32,33]. However, *S*-cathinone can be easily decomposed by light, heat and human enzymes into cathine (1*S*,2*S*(+)-*nor*pseudoephedrine) and 1*R*,2*S*–norephedrine [31]. These metabolites of cathinone demonstrate lower psychostimulant effects due to their less lipophilic properties [29].

Khat has often been called 'natural amphetamine' [31] as it has amphetamine-like effects in central and locomotor stimulation via a similar mode of action to amphetamine by inducing dopamine release and inhibiting dopamine reuptake [29,34,35]. The structure of cathinone and its derivatives such as methcathinone are highly similar to amphetamine, but cathinone has half the potency of amphetamine and cathine is 7–10 times less potent [35,36]. During chewing, over 90% of the alkaloids are released from khat material [33] and can be well absorbed through oral mucosa, with absorption efficiencies of 60% and 80% for cathinone and cathine, respectively [37]. In addition to the major phenylethylamine alkaloids, other classes of alkaloids can be also detected, notably merucathinone, pseudomerucathine, merucathine [38] and the highly complex cathedulins [39].

Several reports detailing a wide range of effects on khat chewers have been published and these include hypertension and arrhythmia due to CNS stimulation [40], alertness, insomnia, anxiety, dizziness, anorexia (a typical amphetamine-use condition), impairment of concentration, irritability and even paranoid psychosis [29]. A review by Odenwald [41] has shown that excessive khat use can cause psychotic disorders and only well-controlled research will be able to conclude the psychological effects of short and long-term use of this material. A critical review by Warfa, et al. [42] also suggested that despite a number of case reports of mental disorder from khat use, the association between khat consumption and psychiatric disorder was still ambiguous and well-designed studies are necessary. Chronic use of khat and synthetic cathinone derivatives have been reported to be a risk factor for several diseases, for example acute myocardial infarction [43,44], haemorrhoids [45], acute cerebral infarction [46], duodenal ulcer [47], oesophageal cancer [48], as well as having profound effects on reproductive [49], behavioral and cognitive [36] function. Futhermore, there are a number of acute and chronic liver disease cases associated with khat chewing, especially when taken together with alcohol or other drugs [50,51]. Consumption of khat has also been linked to fatality from impairment of driving ability [52] or serious cardiac disease due to cathinone's activity to inhibit noradrenaline uptake, which may lead to cardiac morbidity as seen in cocaine intoxication [53]. Moreover, several studies reported the addictive potential of khat due to the dopaminergic effects and noradrenaline reuptake inhibition of cathinone [54]. It is notable that khat is still legal in some countries such as the UK and the Netherlands whilst it is banned in a number of countries, including the USA, Canada, France, Denmark, Germany and Ireland [55].

Lophophora williamsii (Peyote)

Lophophora williamsii is a member of the Cactaceae plant family known as peyote or peyotl, and is a well-known psychoactive cactus found in deserts from Central Mexico to Northern Texas [56]. It is available from horticultural specialists in Europe and gardening centres as an attractive house plant. Its traditional use is ancient and it has been widely used in ethnomedicine for over 5700 years to treat influenza, joint pain, toothache, intestinal disorders, diabetes, snake and scorpion bites, skin diseases, blindness, neurasthenia, hysteria and asthma [56–58]. Peyote is famous for its sacramental use by the Native American Church since the 16th century due to the visual hallucination of

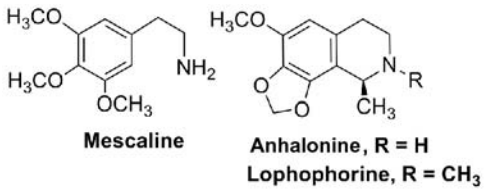


FIGURE 14.6 Mescaline and other components of Peyote, San Pedro and Peruvian Torch cacti.

mescaline, the major phenylethylamine alkaloidal component (Fig. 14.6). Peyote is banned in the USA except for religious purposes whereas in the UK, it is legally sold online and in head shops as fresh or dried plant material. The most common route of administration is by ingestion in forms of fresh or dried buttons, dried powder, capsule or as a tea [59]. Adverse effects experienced by most users are hallucinations, alteration of consciousness and perception, physical reactions such as 'respiratory pressure' and muscle tension can occur and nausea and induction of vomiting (emesis) due to its bitter taste. The hallucinogenic activity and effects in autonomic functions of mescaline are similar to those of LSD, psilocin and psilocybin but with longer onset and duration [16,60]. The principal hallucinogenic constituent is mescaline (3,4,5-trimethoxy-β-phenylethylamine) (Fig. 14.6) and is found up to 6% of dried-button weight [57]. The chemistry of peyote has been extensively studied, and a large spectrum of alkaloids with over 60 different structures from the phenylethylamine and tetrahydroisoquinoline groups, such as anhalonine and lophophorine have been reported (Fig. 14.6). Fresh buttons of peyote can contain up to 8% of total alkaloids [58] and these accumulate with age.

Many studies on *L. williamsii* highlight its taxonomy and traditional use rather than pharmacological activity. The use of peyote and mescaline is uncommon although the clinical effects are significant and can necessitate medical intervention. However in a series of recent case reports, no life-threatening toxicity was observed. Only mild to moderate reactions including hallucinations, tachycardia, agitation and mydriasis were reported [61]. The symptoms of mescaline along with many other plant-derived psychoactive compounds have been reviewed. The acute toxicity of mescaline was not as severe as some other natural psychoactive substances mentioned in the review; however, there was a fatal case resulting from peyote consumption [62]. Moreover, there was a report that an inappropriate use of mescaline during pregnancy for religious purpose was associated with fetal abnormality [63]. Studies on the combination of peyote components are needed, particularly the ability of compounds such as hordenine to modulate mescaline activity. The quinoline alkaloids anhanoline and lophophorine are effectively 'masked' phenylethylamines (compounds which have the phenylethylamine moiety within their structure) and further work on their psychoactive properties is also warranted.

Trichocereus Species

Apart from *L. williamsii*, there are two other popular psychoactive mescaline-containing cacti in the genus *Trichocereus*, which are *Trichocereus pachanoi* (*Echinopsis pachanoi*) and *Trichocereus peruvianus*. These are known as the 'San Pedro' and 'Peruvian Torch' cacti respectively. These cacti are native to the Andean region of South America and are commonly used in shamanistic treatments by decoction of sliced pieces of the cacti [4,59,64]. Although they are one of the most popular legal highs [2,59], there are very few studies relating to their chemistry, activities and toxicity. Mescaline is a major component and the key constituent contributing to their psychoactive activities. *T. pachanoi* was found to contain mescaline at approximately 0.12% of fresh plant [64] and from 0.33% to 2.37% by dry weight while the mescaline content of dried *T. peruvianus* was found to vary from 0% to 0.82% [4]. A recent study quantifying mescaline concentrations in 14 taxa/cultivars of plants in *Trichocereus*

showed that *T. pachanoi* (Matucana) contained the highest mescaline concentration (4.7% of dry weight) whilst *T. peruvianus* contained only 0.24% of mescaline [65,66]. This study can clearly explain why *T. pachanoi* was the selected plant among the *Trichocereus* species in indigenous practice, with users selecting this particular species. Only mescaline has been the main focus in the majority of studies on the San Pedro cactus and much further chemical analysis and biological evaluation remains to be completed.

Mitragyna Speciosa

Mitragyna speciosa Korth. (Rubiaceae) is a psychoactive plant grown in Southeast Asia, especially in Thailand and Malaysia where it is called 'kratom' and 'Biak-Biak', respectively. Growing and buying kratom in the source countries is illegal whilst in several western countries it is freely purchased and appears to be widely used and the most commonly sold legal highs identified in 2011 [3]. Traditionally, Kratom has been used an analgesic and a material to reduce fever [67]. It has potential medical use as an alternative for chronic pain and opioid withdrawal self-therapy due to the opioid agonist activity of the major alkaloids in kratom [68,69]. It is commonly used by workers during physical labour to increase stamina and endurance and as a substitute for opium in Thailand and Malaysia [70]. Kratom is sold in various forms including fresh and dried leaves, powder or a resinous extract which is the main form of NPS (Fig 14.7) in the UK.

A common route of administration is by chewing the fresh leaves at a dosage of normally 10 to 30 leaves per day. Kratom can be ingested as crushed dried leaves by taking powder, drinking as a tea or by smoking the leaves or the extract [71]. Mitragynine (Fig. 14.8) is the major alkaloid (up to 66% in the extract) in kratom, and is the principle compound responsible for analgesic activity due to its potent opioid agonist property [70,72]. Although mitragynine can act on the mu (μ)- and kappa (κ)-opioid receptors, it is structurally different from morphine and other opioid narcotic pain-killers. Mitragynine and its analogues in kratom are indole alkaloids of the *Corynanthe*-type possessing a monoterpene (iridoid) moiety. The mitragynine concentration in kratom leaves from Malaysia (12%) has been found to be less than the leaves from Thailand (66%) [70]. Several 9-methoxy-*Corynanthe*-type monoterpene indole alkaloids are also present

FIGURE 14.7 (A and B) Legal high samples of kratom (*Mitragyna speciosa*) resin.

as constituents in *M. speciosa* leaves and these include speciogynine (7%), paynantheine (9%), speciociliatine (1%) (Fig. 14.9) [70].

Recently, 7-hydroxymitragynine (Fig. 14.9), a minor constituent (2%) of *M. speciosa*, was isolated and demonstrated potent antinociceptive activity in mice. It is now considered to be a major contributory factor for the analgesic properties of *M. speciosa* due to its selectivity for μ- and κ-opioid receptors. The presence of an hydroxyl group at C-7 increases the potency of 7-hydroxymitragynine to be 13- and 46-fold higher than morphine and mitragynine, respectively [70,73]. This clearly indicates that this is

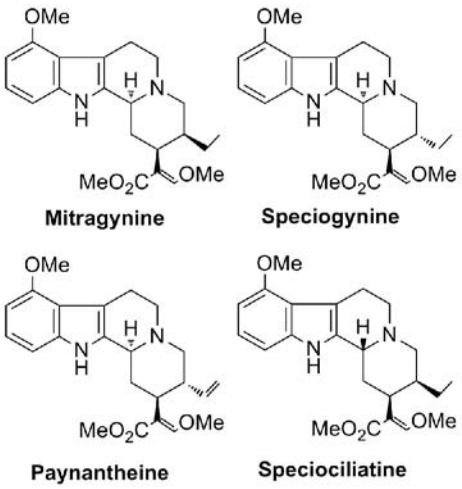


FIGURE 14.8 Mitragynine and related indole alkaloids are the main psychoactive constituents of kratom.

FIGURE 14.9 7-hydroxymitragynine is a recently characterized psychoactive component of *Mitragyna speciosa*.

one of the main pharmacological markers of kratom products' quality and potency.

In addition to analgesic activity, mitragynine is also a key component for the anti-inflammatory properties of kratom by suppressing prostaglandin E2 (PGE-2) production in the cyclooxygenase 2 (COX-2) pathway [73]. Whilst kratom is reputed to be a potent analgesic, it has also been shown to demonstrate a wide range of adverse effects. Opioid-like adverse effects have been observed and include constipation, dry mouth and loss of appetite [74]. There have also been reports of patients suffering from intra-hepatic cholestasis after two weeks of kratom use [71] and seizure and coma [75,76] which might result from opioid agonist action of the major components in kratom. Currently, information on the safety of using this material is scarce but there have been studies in mice showing serious conditions after administration, for example, elevated blood pressure and hepatic enzymes after a single dose [74], impaired cognition and behaviour from long-term use [77] and acute lethally hepatotoxic and mild nephrotoxic effects after high dose administration [74]. Kratom extracts and mitragynine have also been shown to possess cytotoxicity to some human cancer cell lines namely SH-SY5Y cells (neuronal cells) [78].

Whilst kratom metabolites could have the potential to be developed as new therapeutic agents, for example for pain and narcotic withdrawal treatment, there are of course possible serious adverse effects of these materials including potential addiction [79]. Despite the increasing use of kratom, reports of severe toxicity in the literature are rare and its adverse effects are not well understood [71]. A report of liver toxicity [80] and a combination of mitragynine and *O*-desmethyltramadol have been published [81] as has a case of seizure and coma recently reported following kratom use [75].

A study looking at 'kratom dependence syndrome' has suggested that as it is a short-acting μ-opioid receptor agonist, therapeutic agents such as dihydrocodeine and lofexidine are effective

in aiding detoxification [82]. Further studies on kratom toxicology and other natural NPS are crucial to understand the harms associated with this material due to their increasing popularity.

Argyreia nervosa (Hawaiian Baby Woodrose)

Argyreia nervosa syn. *Argyreia speciosa*, also known as Hawaiian baby woodrose, elephant creeper and woolly morning glory, is a large climber in the Convolvulaceae plant family and is a relative of the morning glories and bindweeds [83]. In Ayurvedic medicine, every part of the plant including the seed, leaf, bark and root have usage as they possess a broad-range of pharmacological activities such as antimicrobial, antidiarrhoeal, hepatoprotective, anticonvulsant, antioxidant, aphrodisiac, immunomodulatory, analgesic and anti-inflammatory activity [83]. The seeds are the main NPS materials used as a hallucinogen, and have been used traditionally in a number of diseases in India because of their hypotensive, spasmolytic and anti-inflammatory properties while in Hawaii they are used for religious and sacramental purposes [83].

A. nervosa is recognised as a plant containing lysergic acid amide (LSA), also known as ergine (0.04% by weight) (Fig. 14.10) [84], a precursor to lysergic acid diethylamide (LSD, LSD-25), a well-known synthetic hallucinogenic substance and controlled drug of abuse.

However, neurological effects of LSA are similar to those of scopolamine and not to LSD despite the high degree of similarity between both structures (Fig. 14.10). The major components in seeds of *A. nervosa* are alkaloids (0.5–0.9% by weight) [85], mainly the ergoline-type alkaloids including ergine (d-lysergic acid amide, LSA) and isoergine (l-lysergic acid amide, the isomer of LSA). These two natural products are found in the highest percentage at 0.136% and 0.188%, respectively, of total alkaloids along with ergometrine, lysergol, isolysergol and chanoclavine [84,85]. The amount of indole alkaloids

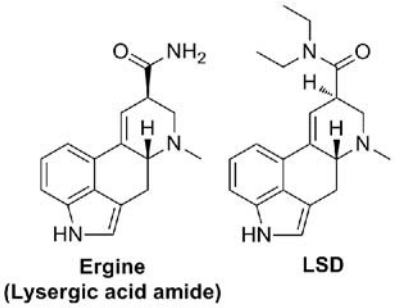


FIGURE 14.10 Lysergic acid amide (ergine), a component of Hawaiian baby woodrose is structurally similar to LSD.

present in Hawaiian baby woodrose seeds is the highest among plants in the Convolvulaceae plant family [85] and 10-fold greater than that of *Ipomoea violacea* (Morning Glory), a related psychoactive plant in the same family.

NPS users consume on average five to ten seeds of Hawaiian baby woodrose, which is equivalent to 0.14% LSA by weight [4,86], by swallowing the whole or crushed seeds as well as drinking an alcoholic extract or an infusion. This material is sometimes used together with marijuana [87]. Reports from users say that the seeds generate LSD-like actions affecting all sensations, nausea, vomiting, mydriasis, impaired motor skills, along with tranquillising effects which can last for as long as six–eight hours [86,88]. Hawaiian baby woodrose seeds can often be confused with the seeds of *I. violacea* which are normally dosed at 100–300 seeds (0.02% LSA) [4]. Ingesting more than 12 seeds of *A. nervosa* can cause highly unpleasant effects such as agitation and tachycardia to fatal doses where the LD_{50} of seed extract is 500 mg/kg of body weight [4,87,89]. There have been a number of clinical reports of toxicity with reports describing mild to serious adverse effects ranging from nausea, vomiting, tachycardia, hypertension, agitation, disturbances in orientation, visual and auditory hallucination, psychosis and anxiety [86,90]. In one case an individual experienced

hallucinations after ingesting the seeds together with smoking *Cannabis* and he was found dead after jumping from a fourth floor [91].

Banisteriopsis caapi and *Psychotria viridis* (Ayahuasca)

Banisteriopsis caapi is a South American hallucinogenic vine in the Malpighiaceae plant family, and is well recognised as a main ingredient of the famous sacred drink called 'ayahuasca' along with the plant *Psychotria viridis* [92,93]. The brew has been traditionally used by ethnic groups for ritual, medicinal and recreational purposes [94,95]. Over the last decade, the use of ayahuasca has spread outside of South America to some religious groups in the USA and European countries as a NPS material [96]. The beverage is usually prepared by boiling or soaking two or more potent psychotropic plants that are native to the Amazon. The most commonly used plants are the stems of the vine *B. caapi* together with an adjuvant plant for instance the leaves of certain Rubiaceae species such as *P. viridis*, or *Diplopterys cabrerana* (Malpighiaceae; syn. *Banisteriopsis rusbyana*) as well as plants in the Solanaceae family such as *Nicotiana* sp., *Datura* sp. and even *Capsicum* sp [92,97,98]. The major components reported in *B. caapi* are β-carboline alkaloid derivatives (0.05–1.95% of dry weight), which mainly include harmine, harmaline and tetrahydroharmine (Fig. 14.11) [92].

The concentration of alkaloids detected in *B. caapi* depends on its origin and part used. For example, the root was found to contain the highest percentage of alkaloids by dry weight compared to other parts of the same plant specimen [97]. McKenna et al., 1984 [94], reported that Peruvian Ayahuasca possessed a high alkaloid content and an average dose 100 mL of the Ayahuasca drink contained 728 mg of total alkaloids consisting of 467 mg of harmine, 160 mg of tetrahydroharmine, 41 mg of harmaline, and 60 mg of dimethyltryptamine (DMT), the active

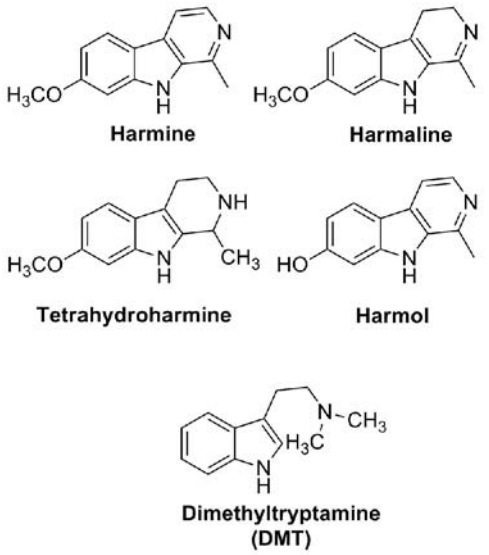


FIGURE 14.11 β-carboline and tryptamine alkaloids of 'Ayahuasca'.

constituent in the admixture plant, which is normally *P. viridis* (Fig. 14.11) [94].

The β-carboline harmaline-type compounds are useful as markers for the identification and standardisation of *B. caapi* samples [98]. Apart from the religious and recreational use of *B. caapi*, it has been shown to have potential for the treatment of neurological disorders. According to Samoylenko et al., 2010, harmine and harmaline demonstrated potent *in vitro* inhibitory activity against monoamine oxidase (MAO)-A and -B enzymes in human brain as well as having the ability to stimulate dopamine release [98,99]. Additionally, proanthocyanidins (−)-epicatechin and (−)-procyanidin that are also present in *B. caapi* showed potent moderate MAO-B inhibitory activities and antioxidant properties which is helpful for the protection of neuronal cell damage from oxidative free radicals [98]. These results support the use of *B. caapi* stem extract for as having potential as a lead for the development of novel therapeutics for Parkinson's disease and other neurodegenerative disorders [100].

Safety data for the use of ayahuasca is scarce. Reported adverse effects include nausea, vomiting, moderate cardiovascular effects such as alteration in blood pressure and heart rate, alertness, hallucinations and anxiety [92,101]. Recently, the addiction to ayahuasca preparations has been assessed using the Addiction Severity Index (ASI) score which suggested that there was no association between ayahuasca use for religious purpose and typical psychological consequences caused by other drugs of abuse [102].

P. viridis, a shrub classified under the Rubiaceae plant family, is one of the plants frequently used as an admixture to synergise with the effects of *B. caapi* in the ayahuasca drink [103]. The leaves of *P. viridis* and other adjuvant plants are used to prepare the drink which contains a major psychoactive indole alkaloid *N,N*-dimethyltryptamine (DMT) (Fig. 14.11), a practically ubiquitous natural product in many species of Leguminosae [94]. The total alkaloid concentrations detected in the leaves of *P. viridis* ranged from 0.1 to 0.66 % of dry weight [94,97]. DMT is known as a potent hallucinogen, and its structure closely resembles that of serotonin, our endogenous monoamine neurotransmitter and produces similar effects via the various serotonin receptors. Ingesting DMT can cause mood swings and visual, auditory, sensational and perceptual alterations [104]. However, DMT is orally inactive as an hallucinogen since peripheral monoamine oxidase (MAO) can break down DMT before reaching the central nervous system [92,94]. Therefore, it has to be taken together with a plant containing an MAO inhibitor like *B. caapi* to prevent DMT degradation [92]. The combination of these two plants helps to synergise the psychoactive effect.

It has been found that *P. viridis* samples in markets contain a wide range of alkaloids and some samples had only minute or undetectable amounts of DMT [105]. DMT is classified as a Schedule I Controlled Substance in the USA and is a Class A controlled drug in the UK [103,106], but it is worrying that many plants containing DMT can be readily bought online or in head shops in different forms without any form of regulation.

Fatal toxicity of ayahuasca preparations have been recorded with subsequent analysis showing the presence of *Psychotria* and *Banisteriopsis* natural products [107]. The risks of ingesting plant materials which drastically effect perceptual alterations are obvious especially visual hallucinations. An Internet survey concluded that the online vendors of ayahuasca preparations did not provide any advice or instructions on usage with regard to safety and toxicity and certainly no indication that these materials could interact with other drugs [108].

A study looking at the risks associated with oral use of *N,N*-dimethyl tryptamine (DMT) and harmaline alkaloids has concluded that their safety margin is comparable to codeine, mescaline or methadone. The risk of sustained psychological disturbances is minimal as the prevalence rate was approximately 1.3 % [109].

Ayahuasca preparations have also been proposed as potential treatments for drug addiction however too few studies have been conducted to substantiate this [110].

Salvia divinorum ('Psychedelic Sage')

Salvia divinorum L., a plant in the Lamiaceae family and native to the Mexican Mazatec, is a prominent NPS product being sold on UK websites in the forms of live plants, dried leaves and extracts in the name of 'Salvia' [2]. *S. divinorum* is an attractive horticultural plant (Fig. 14.12) and is variously known as Psychedelic sage, Salvia, Diviner's sage, Ska Maria, Ska Pastora, Hojas de Mariais and Hojas de Petora [111].

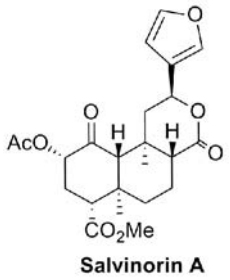
The plant is exceptionally easy to cultivate and, like culinary sage (*Salvia officinalis*), it can be cultured with cuttings with compost, not even requiring rooting hormone. Traditionally, the Mazatec used these leaves as a potent hallucinogen which was administered by either chewing, drinking or smoking [112]. Recreational users of

FIGURE 14.12 The flowers of *Salvia divinorum* (Lamiaceae), a popular UK legal high.

this NPS normally ingest an infusion or the fresh leaves of *S. divinorum*, or the material is smoked causing both a rapid onset and a short duration of the hallucinogenic effect [113]. Users report depersonalisation, laughter, weightlessness and self-consciousness disappearing within 30 minutes of usage [114]. There are limited data on the clinical effects of this material and *S. divinorum* may have long-term effects such as déjà vu and a recent review discusses evidence for potential abuse [115].

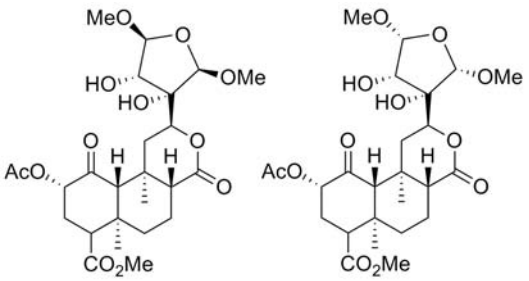
Salvinorin A, a non-nitrogenous *neo*clerodane diterpene (Fig. 14.13), was determined as the key active substance for the psychoactive activity due to its selective κ-opioid receptor (KOR) agonist properties.

Salvinorin A was found to be the first non-alkaloidal KOR selective drug having a unique structure being different from previous known hallucinogens [116] and was regarded as a potent hallucinogen equivalent to the synthetic lysergic acid diethylamide (LSD; LSD25) and 4-bromo-2,5-dimethoxyphenylisopropylamine (DOB) [112,116]. *S. divinorum* also contains a whole range of other diterpenoid compounds and the chemistry of this species is becoming better delineated [111].



Salvinorin A

FIGURE 14.13 Salvinorin A, a kappa-opioid receptor agonist from the 'Psychedelic sage' *Salvia divinorum*.



Salvinicin A **Salvinicin B**

FIGURE 14.14 Salvinicins A and B from *S. divinorum* are partial κ- and μ-opioid receptor agonists.

Only salvinorin A has been demonstrated to have high KOR affinity and the methyl ester and furan ring were found to be essential for its activity. However, there are recent reports concerning the biological activity of two new *neo*cleodane diterpenes, salvinicins A and B (Fig. 14.14) as partial κ- and μ-opioid receptor agonists respectively, but their relevance to the hallucinogenic activity of *S. divinorum* is still unclear [111,117].

Due to its KOR agonist ability, *S. divinorum* is proposed to demonstrate the pharmacological activities relating to the KOR, for example, analgesia, sedation and depressant effects and this has an implied potential utility in the treatment of insomnia, schizophrenia, depression, the hallucinations associated with dementia, for example, Alzheimer's disease, and as a

potential aid to help with amphetamine- and opiate-withdrawal symptoms [116].

Toxic psychosis has been observed after ingestion of salvinorin A [118]. Users report an intense high associated with consumption but the harms associated with Salvia use are poorly understood due to a paucity of toxicological data and the risks associated with this are that users may feel that the material is consequently safe due to a lack of adverse reports. The strong psychotic effects of Salvia could put users at risk due to impairment of judgment [119]. However, the plant does not appear to be addictive and users tend not to make repeat purchases [3]. A number of products are appearing on Internet sites marketing concentrated materials, for example ×10 or ×15 strength, but this does not relate in any way to rigorous phytochemistry and users should be wary of purchasing such materials as they have not been standardised on the main psychoactive material, salvinorin A. There are risks associated with these concentrated forms if the extracts turn out to be much higher in salvinorin A concentration. For a concise review of the science including the chemistry, pharmacology and toxicology of *S. divinorum* the reader should consult Prisinzano [120].

CONCLUSIONS

Natural product NPS offer many challenges in terms of analysis of their chemistry and assessment of their pharmacology and toxicology. Firstly in acquiring crude plant or fungal material, the user has little idea of the true botanical or mycological identity of the material, with substitution being a real possibility. This could be further compounded by spraying of the crude drug with a synthetic psychoactive compound as was seen with the Spice smoking mixtures being adulterated with synthetic cannabinoid receptor agonists.

Natural materials are inherently variable in terms of their chemistry with many factors such as weather, soil, geographic location, effects by microbes and herbivory effecting the concentration of natural products within a sample and therefore having the opportunity to drastically change the biological properties of this material. This is further complicated by the existence of chemical races within a single species, where the chemistry may be different from once race to another.

Some herbal NPS are also marketed as extracts, with examples such as kratom and Salvia being popular. The type of extraction methodology used will drastically affect the phytochemical quality of the end product, and if the manufacturers have no idea of the merits of an extraction protocol, they are likely to produce extracts of high variability. Some extracts are marketed as ×5, ×10 or ×15 but this is a meaningless concentration factor as it does not take in to account standardisation of the extract on a psychoactive component, for example salvinorin A or mitragynine.

There is also the temptation that NPS suppliers will adulterate an extract at the point of its manufacture, thereby adding a further level of complexity to the area and potential drug–drug interactions.

Natural product NPS materials are exceptionally complex in terms of their chemistry. This greatly enhances the complexity of their biology with a paucity of data relating to the toxicology of these materials, and even less regarding their interactions with conventional drugs of abuse such as cocaine and other stimulants. The level of complexity, variability, the unknown nature of these samples, coupled with the risks associated with taking psychotic materials, particularly the hallucinogenic tryptamine-containing materials, could offer further risks of ill health by misadventure, with potentially life-threatening consequences.

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