

NEW TRENDS in HERBAL DRUGS of ABUSE

Jochen Beyer, on behalf of the IATDMCT Young Scientists group

INTRODUCTION The use of psychoactive plants for mind-altering purposes has a long tradition. Archaeological evidence shows the use of psychoactive plants by humans for thousands of years, with use in a highly ritualized and ceremonial context often suggested.¹⁰ Recently, the presence of a psychoactive compound in a 5700 year old dried cactus “button” found in a cave in Texas has strengthened the evidence that humans recognized the psychoactive properties of plants at that time.⁵ *Papaver somniferum* was described as the “plant of happiness” on a Sumerian tablet.¹³ Much evidence of the medical use and abuse of opium can be found in Egyptian, Greek, and Roman reports between 3000 and 1000 BC.¹⁰ In the middle Ages the Arabic scientist Avicenna (980 – 1037) and the German abbess Hildegard von Bingen (1098-1179) described numerous plants and their effects, including their psychoactivity. The description of plants including their psychoactivity was mainly investigated in the 16th century by the so-called founding fathers of botany; Hieronymus Bock (1498-1554), Leonhart Fuchs (1501-1566), and Otto Brunfels (1488-1534). The first published systematic study of psychoactive plants was published in 1855 from Heinrich von Bibra. His book described 17 plant narcotics and stimulants, including their effects on the human body.¹³

The abuse of herbal drugs initiated the first treaty of international drug control. In 1912 the International Opium Convention was signed by 13 countries to provide control over the distribution of morphine and cocaine. In 1925, the convention was revised by the addition of the prohibition of hashish due to its common abuse. Today, many herbal drugs of abuse are controlled by national and international conventions.

The manner of abuse of herbal drugs has recently changed. Although the common drugs of abuse, like cannabis, opioids, and cocaine, are still popular, more and more drug users try to obviate drug regulations by abuse of “new herbal drugs”. The source of knowledge is often internet based; “trip reports” and descriptions of the plants are shared among drug users. Often, the new herbal drugs are falsely propagated as safe and legal. This article shows some new trends in herbal drug abuse by describing some plants and their usage and pharmacology.

1. NIGHTSHADES The botanical family of nightshades contains edible as well as poisonous plants. Well-known poisonous plants, such as *Atropa belladonna* (deadly nightshade), *Datura stramonium* (thornapple), and *Brugmansia spec.* (angel’s trumpet) have been used for their psychoactive properties for hundreds of years. Common names such as dwale, death’s herb or witch berry give an impression of their toxicity and use in the Middle Ages.

The toxicity and pharmacological effects of deadly nightshade, for example, are also part of the etymology of the botanical name. The genus *Atropa* is named after the goddess Atropos, who is known in Greek mythology to cut the life thread. The species name *belladonna* is Italian for “beautiful lady”, and originates from the historical use of its berry juice by women to dilate their pupils.⁶

Many plants of this family contain toxic tropane alkaloids like (S)-(-)-hyoscyamine and (S)-(-)-scopolamine. Even though only (S)-(-)-hyoscyamine is present in the plant, this substance is converted to a racemic mixture of 50% (S)-(-)-hyoscyamine

and (R)-(+)-hyoscyamine, called atropine. This conversion is a result of either extraction or release after ingestion. Atropine and scopolamine act pharmacologically by blocking acetylcholine receptors of the muscarine subtype. The blockage of these receptors cause symptoms such as tachycardia, dilated pupils, decreased gastrointestinal motility, dry hot skin, and dry mouth due to decreased sweat and saliva production. Apart from these peripheral effects, atropine also affects the central nervous system, causing agitation, disorientation, and hallucinations.¹⁴ Due to the hallucinogenic properties of these alkaloids, plants are often abused. This increasing misuse for example has prompted a prohibition by law in Florida of planting angel's trumpets.

2. AYAHUASCA Ayahuasca is the name of a psychoactive beverage which has its origin in the Amazon region. The name means "vine of the souls" in Quechua, a native language of South America. Traditionally ayahuasca is prepared by boiling or soaking the stems and bark of *Banisteriopsis caapi* together with various plants containing the psychoactive alkaloid *N,N*-Dimethyltryptamine (DMT). The most commonly used plant containing DMT is *Psychotria viridis*. DMT is a potent short-acting hallucinogenic agent, but is not active following oral ingestion of doses up to 1000 mg. After parenteral administration, doses of more than 25 mg are psychoactive. The alkaloid is quickly metabolized via monoamine oxidase (MAO) to inactive metabolites.

The stems and bark of *B. caapi* contain β -carbolines like harmine and harmaline. These carbolines are not psychoactive, but they are inhibitors of the enzyme MAO. The combination of these plants is psychoactive because the breakdown of the psychoactive DMT is inhibited.⁹

Recent trends use this pharmacological "trick" to provide an orally available source of DMT by using other MAO inhibiting drugs. These combinations are often called pharmahuasca.

3. MORNING GLORY & LYSERGIC ACID AMIDE Morning glory is a common name for over 1,000 species of plants in the family *Convolvulaceae*. If the term morning glory is used for herbal drugs of abuse, the name mainly refers to *Ipomea tricolor* and sometimes to *Rivea corymbosa*. Both plants are perennial twinning liana native to Middle and South America. The seeds of both plants have been used by Native Americans for their hallucinogenic properties. The fresh or dried seeds are ground, mixed with water and ingested orally. After ingestion, the seeds produce psychedelic effects similar to those of *Psilocybe* mushrooms or LSD. The hallucinogenic effects of a cold water extract are not exactly the same as those of LSD, as visions of "small people" are typical. Eating the seeds can induce side effects such as nausea and vomiting, probably induced by non-water soluble alkaloids.¹³ In 1960, Albert Hofmann isolated ergot alkaloids such as the lysergic acid amide from *R. corymbosa*.⁷ Lysergic acid amide, also called ergine, has been assayed for human activity, by Albert Hofmann in self-trials back in 1947, well before this was known to be a natural compound.¹⁶

4. EPHEDRA & KHAT The genus *Ephedra* includes approx. 45 species that are indigenous to the temperate and subtropical regions of Asia, Europe and America. The species *E. sinica* has been used in Traditional Chinese Medicine with the name Ma Huang for more than 500 years. The use of Ma Huang as a stimulant was first documented in the time of the Han Dynasty (ca. 206 BC-220 AD).³ The main pharmacologically active ingredients of the *Ephedra* species are the alkaloids ephedrine and pseudoephedrine. These compounds are potent central nervous system stimulants and

also have sympathomimetic effects on the peripheral nervous system.¹⁴ Because of their peripheral effects, ephedra alkaloids are often contained in cold medications. Recently, the use of pseudoephedrine in cold medications has been banned in many countries because the alkaloid is used as a precursor in the synthesis of the designer drug methamphetamine.

Catha edulis, commonly known as khat is botanically not related to *Ephedra*. Khat is indigenous to Ethiopia, and today it is cultivated in Arabia, some African countries, and Afghanistan. The fresh leaves are chewed as soon as possible after harvesting.¹³ Large quantities of fresh leaves are illegally imported to other countries. The leaves have to be consumed fresh and not older than two days as the psychoactive properties of the leaves decrease rapidly after harvesting. The active ingredients of khat are similar to those contained in *Ephedra*. Beside the ephedra alkaloids norpseudoephedrine and norephedrine, khat contains the alkaloid cathinone.¹¹ The pharmacological properties of khat are amphetamine-like.⁸ Due to khat abuse, the plant and its ingredients cathinone and norpseudoephedrine are controlled substances in many countries.

5. NUTMEG Nutmegs are the seeds of the evergreen tropical tree *Myristica fragrans*, indigenous to the Spice Islands. The seeds are covered by a net-like red aril which is used to produce mace. Both seeds and mace are mainly used as a spice, but the seeds are psychoactive when administered in high doses. The psychoactivity of nutmeg is supposedly caused by constituents of its volatile oil, which are the alkenebenzene derivatives elemicin, myristicin, and safrole. In 1966, Shulgin hypothesized that the possible psychotropic effects of myristicine may be caused by the metabolic addition of ammonia to the allyl side chain, leading to the amphetamine derivative MMDA¹⁷ and that of elemicine by conversion to the designer drug TMA. Although this metabolic step is unlikely, a formation of these designer drugs would explain the psychoactive effects of nutmeg. This hypothesis has been widely accepted despite that the formation of these designer drugs in humans has never been proven. Recently, a study has shown that these proposed metabolites could not be detected in human and rat urine after ingestion of large amounts of nutmeg and the isolated ingredients itself.² Further studies to explain the psychoactive effects of nutmeg are needed.

6. SALVIA DIVINORUM *Salvia divinorum* is a herbaceous plant native to the Mazatec region of the Sierra Madre Oriental in the Mexican state Oaxaca. This plant has been used in traditional spiritual practices by Mazatec natives in a manner very similar to magic mushrooms (*Psilocybe spec.*). Albert Hofmann tried to discover its psychoactive constituents by analyzing the juice pressed from the plant.¹³ His analysis was unsuccessful and it took until 1982 to isolate the diterpenes salvinorin A and salvinorin B. So far, 14 diterpenes have been isolated from *Salvia divinorum*, but salvinorin A seems to be the major active compound. In 1994, Daniel Siebert reported that the leaves of *S. divinorum* have psychoactive effects when the ingredients of the juice are absorbed via oral mucosa.¹⁸ The plant material is inactive when swallowed as quickly as possible to bypass the oral mucosa. Some years later, in 2002 salvinorin A was found to be a potent (and the first non-nitrogenous) agonist of the κ -opioid receptor,¹⁵ whereas salvinorin B is inactive at this receptor. A study in 2004 has also confirmed κ -opioid receptor agonist-like discriminative effects in rhesus monkeys.¹² During that time, the availability of the plant increased rapidly, partially due to internet trading. Within a few

years, *Salvia divinorum* became a very popular herbal drug of abuse. The unique pharmacology of salvinorin A as the first non-nitrogenous opioid receptor agonist and its popularity as a drug of abuse has massively increased the interest for researchers. More than 60 papers on salvinorin A have been published in the last 3 years.

7. KAVA The common English name for the western pacific plant *Piper methysticum* is kava. Other names for the plant are ‘awa’, used in Hawaii, or ‘yaqona’, common in Fiji. Kava is an evergreen bush growing up to 3 m tall, with heart-shaped leaves up to 20 cm in length. In 1777, the plant was first described botanically by Johann Gregor Forster, a companion of Captain James Cook. During this trip, they also described the psychoactivity of the plant and the ceremonies of the indigenous Polynesians. The psychoactivity of kava is also indicated by the scientific species name *methysticum*, which is Greek for intoxicating. Today, kava is the most important psychoactive plant in Oceania and in aboriginal cultures in the Northern Territory of Australia.⁶ Traditionally Kava is prepared by grinding or chewing the rhizome, which is mixed with water or coconut milk. The effectiveness of kava and kava ingredients in the treatment of anxiety has been shown in clinical studies. Therefore, extracts of the plant have been introduced into modern medicine as a mild anxiolytic. After the report of some deaths due to its medicinal use, kava medicines have been banned, as they are suggestive of causing acute liver failure.¹ The traditional use of kava by Pacific Islanders and by some aboriginal communities is not believed to be associated with liver damage. A recent study has shown that kava feeding in rats does not cause liver damage.⁴ Further investigations are necessary to demonstrate the long term safety of kava preparations.

CONCLUSION The abuse of herbal drugs has been a part of human culture for many centuries. The potential harm caused by misuse of plants is enormous, and has led to the formation of the International Opium Convention, the first international drug control treaty. Today many common drugs of abuse, including those of herbal origin, are controlled substances. Nowadays, “uncommon” herbal drugs of abuse are becoming increasingly popular amongst drug users, partly as a result of publicity over the Internet. Consequently, these new trends in herbal drug abuse are challenging for both the toxicologist and the legislature. They should be carefully observed by toxicologists to provide a scientific background of abuse in terms of new drug regulations.

ABOUT THE AUTHOR Jochen Beyer was introduced to you in the *Spotlight on New Members* column (2006, Issue 3). He is currently a post-doctoral fellow at the Victorian Institute of Forensic Medicine at Monash University in Southbank, Victoria, Australia. Jochen is also an active member of the IATDMCT Young Scientists group. You can contact him for more information on this article at jochenb@vifm.org.

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