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Review Article

New psychoactive substances of natural origin: A brief review

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ABSTRACT

Plant-based drugs of abuse are as old as recorded human history. Although traditional addictive substances, such as opium, cannabis and coca, have been controlled by the United Nations anti-drug conventions, many, if not most, natural plants with addictive or abuse liability remain elusive. Therefore, the United Nations Office on Drugs and Crime (UNODC) has warned the emerging threat from new psychoactive substances (NPS), which are mostly derived or modified from the constituents of natural origin. For example, synthetic cannabinoids and synthetic cathinones are derived from the cannabis and khat plant, respectively. In this review, we briefly discussed the chemistry, pharmacology and toxicology of five common NPS of natural origin, i.e., khat, kratom, salvia, magic mushroom and mandrake. Through the review, we hope that professionals and general public alike can pay more attention to the potential problems caused by natural NPS, and suitable control measures will be taken.

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1. Introduction

Abuse of plant-based drugs is as old as humans with opium (the coagulated juice of the opium poppy, *Papaver somniferum* L.), cannabis (the flowering or fruiting tops of any plant of the

genus *Cannabis*, including *C. sativa* and its varieties) and cocaine (the major addictive ingredient in *Erythroxylon coca* and several species in the genus *Erythroxylum*) that were used for pain relief and in religious rituals [1]. However, it was not until the profound aftermath of opium smoking during the Ching

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Dynasty of China in the late 19th Century that eventually led to the enactment of the 1961 Single Convention on Narcotic Drugs [2]. Besides the 1961 Single Convention that dealt with the control of traditional narcotic drugs, the 1971 Convention on Psychotropic Substances and the 1988 Convention against Illicit Traffic in Narcotic Drugs and Psychotropic Substances were subsequently promulgated mainly for synthetic drug control [3,4]. Although these three Conventions still serve as the basis for international drug control, many other psychoactive substances are elusive. They are collectively defined as New Psychoactive Substances (NPS) by the United Nations Office on Drugs and Crime (UNODC) [5].

NPS, with no comprehensively scientific studies on their toxicity and abuse liability, may pose a threat to public health. According to the UNODC Early Warning Advisory (EWA) on NPS, these substances have been indicated a global phenomenon with over 100 countries and territories from all regions of the world. More than 600 substances have been reported as of December 2015 [6]. In the market, NPS have been known by terms such as 'designer drugs', 'research chemicals', 'legal highs', 'herbal highs' and 'bath salts' [7]. While the term 'legal highs' or 'herbal highs' implies that NPS offer as a legal alternative to controlled drugs, 'designer drugs', 'research chemicals', and 'bath salts' are often used to describe the NPS that are chemically synthesized or structurally modified [8].

Although most NPS are synthetic chemicals, many of them are derived from natural products. For example, synthetic cannabinoids and synthetic cathinones, which constitute a majority of NPS items, are analogues of Δ^9 -tetrahydrocannabinol and natural cathinone from cannabis and khat, respectively. In other words, the plant-based substances are usually the origin of NPS but their toxicity remains to be elucidated. Chemical classification of some natural toxins with abuse or dependence liability indicates that most of the active ingredients in the natural NPS are alkaloids (Table 1). To prevent redundancy, the traditional plant-based drugs, such as opium, coca and cannabis, which have been thoroughly explored, will not be reviewed. Instead, this review will focus on plant-based NPS to discuss their chemistry, pharmacology, and toxicology.

2. Materials and methods

The NPS of natural origin, or plant-based NPS, is one of the 9 NPS groups as defined by UNODC [5]. In order to review the

NPS of natural origin, similar keywords such as plant-based drugs, natural origin drugs, new psychoactive substances and addicted/abuse were selected and searched from literature on the Pubmed, Web of Science (WOS), DrugBank and other websites. Studies were included if they were plant-based NPS according to UNODC classifications. Five common NPS of natural origin, including khat, kratom, salvia, magic mushroom and mandrake, were systematically explored by chemistry, pharmacology and toxicology in this study.

3. Chemistry, pharmacology and toxicology of NPS of natural origin

3.1. Khat

Khat (*Catha edulis*, Celastraceae), whose traditional names include kat, Kafta, qat, qaad, ghat, chat, tschat, miraa, Abessinischer Tee, Abyssinian Tea, Somali Tea and Arabian Tea, is a plant native to the Horn of Africa and the Arabian Peninsula [6]. A 'katin' alkaloid was identified first in 1887, 'cathine' in 1930 and 'cathinone' in 1975 [7]. In Yemen, people usually consume khat by chewing its leaf and shoot [8]. After chewing, cathinone and cathine alkaloids can be released for psychoactive effects [9]. In recent years, the alcoholic extracts of khat sold as 'herbal highs' has also been reported [10].

According to the report of EU Member States from 2009 to 2012, khat was the second most popular plant-based substance after *Salvia divinorum* in Europe [10]. In the past, khat was usually consumed by migrant communities from Ethiopia, Kenya, Somalia and Yemen. But recently, its use has distributed over these communities. In 2009, Canada, Ireland, Italy, New Zealand, Norway, the United States and Hong Kong reported khat emerged in their illicit drug markets. Khat is under national control in some, if not most, countries although its ingredients, cathinone and cathine, are listed in schedules I and III, respectively, in the 1971 Convention [10].

3.1.1. Chemistry

There are dozens of alkaloids as well as tannins, flavonoids, glycosides, non-cyclic nitrogen containing compounds, and other compounds identified in khat [11–15]. Of these chemical constituents, the most important group contributing to the stimulant activity of khat is the phenylalkylamines, which have structural resemblance with the neurotransmitters dopamine and norepinephrine [12]. The khat phenylalkylamines constitute at least one cathinone [S-(–)-cathinone], and two diastereomers cathine [1S, 2S-(+)-norpseudoephedrine] and norephedrine [1R, 2S-(–)-norephedrine] (Fig. 1). The structures of these compounds are related to amphetamine and noradrenaline. Khat only contains the (–)-enantiomer of cathinone, whose absolute stereochemistry is identical to that of S-(+)-amphetamine. Besides phenylalkylamines, the other major alkaloid group is cathedulins, which are based on a poly-hydroxylated sesquiterpene framework and are basically polyesters of euonyminol. Sixty-two cathedulins have been identified from fresh khat leaves [16].

Table 1 – Chemical classification of some plant and fungal toxins with abuse or dependence liability.

Chemical Category	Genera	Examples
Alkaloids	Atropa & Erythroxylum	Tropanes (e.g., Atropine and Cocaine)
	Catha	Cathinone
	Mitragyna	Mitragynine
	Papaver	Isoquinolines (e.g., Morphine)
	Psilocybe	Psilocybin, Psilocin
Resins and Resinoids	Cannabis	Tetrahydrocannabinol
Terpenoids	Salvia	Salvinorin A

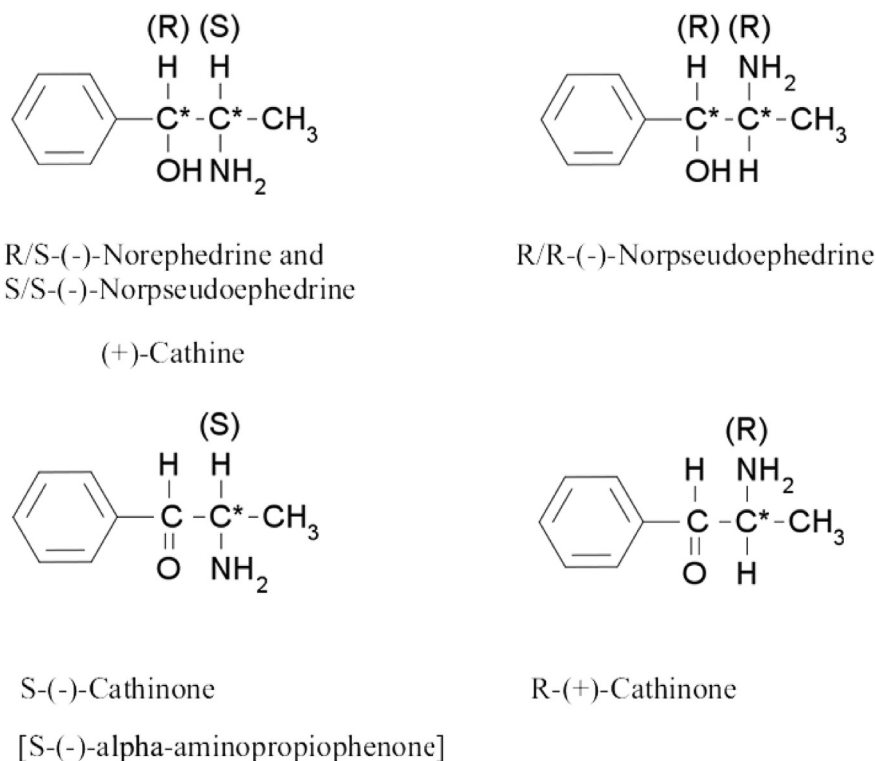


Fig. 1 – Chemical structures of cathinone and cathine.

3.1.2. Pharmacology

The major active constituents in khat could be extracted via chewing and dissolved in the saliva, then absorbed through the buccal mucosa and gastro-intestinal (GI) tract [17,18]. Due to the greater lipophilicity, cathinone is more predominant as a psychoactive agent than cathine or norephedrine [19]. The mechanism of cathinone on neurotransmission is to trigger presynaptic dopamine release and restrain the reuptake of dopamine, which is similar to the effect of amphetamine [20,21]. Cathinone may bind to dopamine and 5-HT receptor sites, although it has the highest affinity for norepinephrine receptors [18,22]. Furthermore, cathinone has also been shown to induce serotonin release and inhibit its reuptake [23].

All cathinones, including natural cathinone and its synthetic derivatives, are inhibitors of the monoamine transporters, but their selectivity for the 5-HT transporter (SERT), norepinephrine transporter (NET) and dopamine transporter (DAT) varies substantially [24]. In addition, most of the cathinones are substrate releasers. However, the molecular pharmacology of cathinones has not yet been fully elucidated. With radioligand binding assays performed in cultured HEK cells, Simmler et al. classified the cathinones into three groups, according to their relative potency to inhibit SERT, NET and DAT, as well as their action as substrate releasers: (1) cocaine-MDMA-mixed cathinones, which are relatively nonselective monoamine uptake inhibitors similar to cocaine; (2) methamphetamine-like cathinones, which are preferential catecholamine inhibitors and DA releasers; and (3) pyrocaleron-cathinones, which are very potent and selective

catecholamine uptake blockers but not substrate releasers [24]. As exemplified in Fig. 2, all listed cathinones share the same basic structure of β -keto-amphetamines, but it would be difficult to correlate the different functions of these three groups with modification of their structures. Further study on the structure-activity relationship of cathinone is needed.

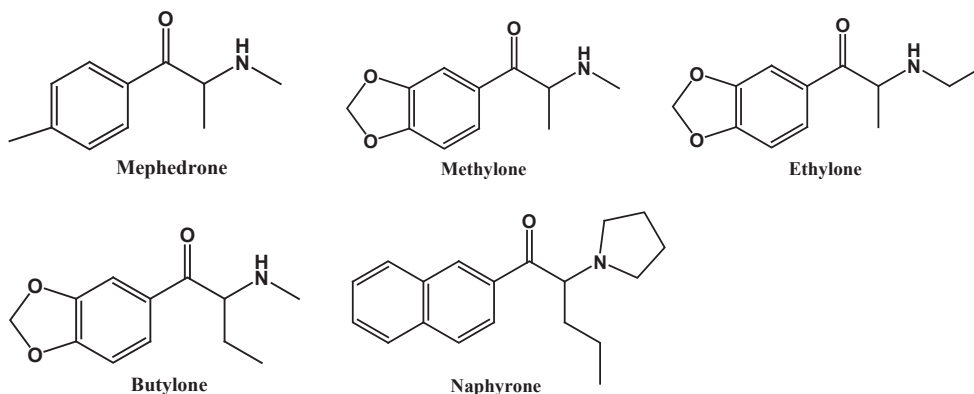
3.1.3. Toxicology

Due to various compounds present in khat, khat chewing may have miscellaneous effects, especially on the GI system and the nervous system. In general, effects on peripheral nervous system could include constipation, urine retention and acute cardiovascular effects, while effects on the central nervous system could include heightened alertness, tolerance, dependence and psychiatric symptoms [12].

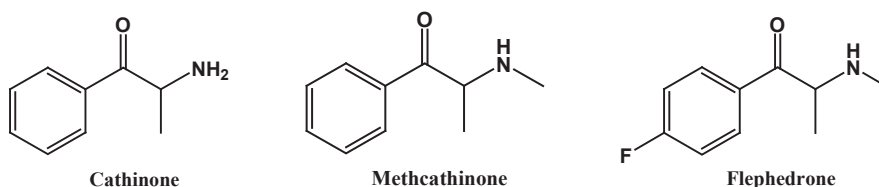
There is still some debate about whether khat use may cause dependence [18]. Kassim et al. assessed 204 khat chewers in Yemen and defined a third of those interviewed met the criteria for dependence [24]. The majority of them had experienced cravings for retaining the drug or trying to reduce their intake. Abstinence can lead to a withdrawal syndrome that includes sleep disorder, depression and sleepiness, as well as temporary hypotension [19]. Because most of the individuals who tried to withdraw or reduce intake of the drug relapsed into their khat habit, it was concluded that khat use caused dependence similar to other drugs of abuse [25].

Khat use may also cause psychological problems. Banjaw et al. [26] reported that khat extract increased baseline aggression in rats, indicating khat induced psychotic episodes [12]. Previous study also found these psychotic

(1) Cocaine-MDMA-mixed cathinones



(2) Methamphetamine-like cathinones



(3) Pyrovalerone-cathinones

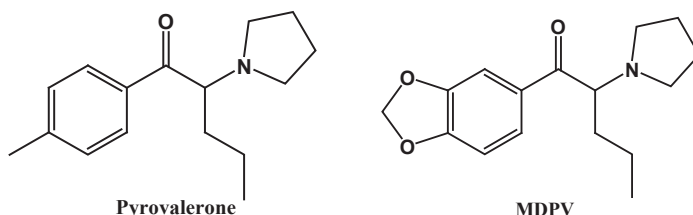


Fig. 2 – Three groups of cathinone structures according to their relative potency to act as SERT, NET and DAT inhibitors, and their action as substrate releasers (modified from Simmler et al., [24]).

symptoms occur rarely and would disappear upon abstain the consumption of khat [18]. However, previously diagnosed or hidden psychiatric conditions may be exacerbated by chewing khat [12,18]. A typical session of khat chewing would result in absorption of effective components that is similar to the effect of 5 mg amphetamine [27]. The pharmacological effects of heightened alertness, euphoria, hyperthermia, anorexia may also increase respiration rate, heart rate, and blood pressure [28], but fatalities associated with khat consumption have not been reported. However, long-term use of khat has been associated with adverse effects from psychiatric disorder to harm of major body organs, and also similar to neurological disorders caused by amphetamine or cocaine use [29].

3.2. Kratom

Kratom (*Mitragyna speciosa* Korth., Rubiaceae), also known as Kas Biak-Biak or Ketum in Malaysia and Kratom, Kakuam, Kraton, Ithang or Thom in Thailand [30–34]. Kratom, a

tropical tree with 4–16 m high, is native to South East Asia, the Philippines and New Guinea, and is also cultivated elsewhere now. People often use fresh kratom leaves to alleviate pain. Depending upon the dose consumption, the effects of psycho-stimulant and opiate-like efficacy have been reported [35,36]. Kratom are consumed by chewing at a dosage of normally 10 to 30 fresh leaves per day, while for the dry powdered leaves it is often swallowed or brewed, but seldom smoked [33]. During long working hours, low kratom dosage has provocative effects against lassitude. However, it can have sedative-anesthetic effects at higher dosages. Kratom is also regarded as an opium substitute in traditional medicine. Phytochemicals, including over 40 structurally related alkaloids and several flavonoids, polyphenols, and various glycosides, have been isolated from various parts of kratom [37]. In the leaves, the primary psychoactive constituents are mitragynine and 7-hydroxymitragynine, both being found only in kratom [38].

In Europe, products labeled as ‘kratom acetate’ or ‘mitragynine acetate’ has been available in the early 2000s [10]. Of the

kratom products, a brand under the name ‘krypton’ has been found to be a blend of caffeine and *O*-desmethyltramadol, an active metabolite of tramadol. In recent years, products containing kratom have been sold as ‘incense’ for their psychoactive effects, but concentrations of these active components vary depending on the variety of kratom used, the circumstance and the time of harvesting. According to the internet surveys by EMCDDA in 2008 and 2011, kratom was one of the most widely supplied NPS [38]. And the answers to UNODC questionnaire on NPS also revealed kratom was on the list of top three plant-based substances, along with khat and *S. divinorum*. Because kratom was not often under surveillance in national drug abuse surveys, the information of the prevalence of kratom use has been limited. Kratom and its active alkaloids are not listed under the 1961 and 1971 Conventions, but several countries have made control policies on kratom, mitragynine and 7-hydroxymitragynine.

3.2.1. Chemistry

There are more than 40 active compounds in kratom [30]. Mitragynine (Fig. 3) is the major alkaloid, which can constitute up to 66% in the leaf extract of kratom. Mitragynine and its analogues, such as mitraphylline and 7-hydroxymitragynine, are indole alkaloids of the Corynanthe-type possessing a monoterpene (iridoid) moiety [33]. Other alkaloids in kratom also include raubasine and some yohimbe alkaloids [39–41]. Kratom contains at least one alkaloid that can block calcium channel and reduces current induced by *N*-methyl-D-aspartate (NMDA) [42,43]. The mitragynine contents in kratom vary with location and season. When kratom tree is grown in Southeast Asia, the content of mitragynine tends to be higher, but in elsewhere it tends to be low or non-existent [44]. Using liquid chromatography-electrospray ionization mass spectrometry (LC-ESI-MS) to analyze the products marketed as kratom leaf, mitragynine was found to contain 1–6% and 7-hydroxymitragynine 0.01–0.04% [45].

3.2.2. Pharmacology

Kratom leaves are traditionally used to treat intestinal diseases, muscle pain, coughing and diarrhea in Malaysia and Thailand [32,36,46–48]. Quite a few studies recommended that kratom products have the effects of analgesic, antipyretic, antitussive, antidiarrheal, euphoric, antidepressant, and

anxiolytic [38]. They may act as immune booster, lower blood pressure, and have anti-viral, anti-diabetes and appetite suppressing effects [49,50].

The pharmacokinetics of kratom in humans has not been well studied. Various pharmacokinetic factors such as metabolic half-life, protein binding property, elimination and metabolism are not yet known [44]. In animal models, kratom has been found with addiction potential when mitragynine and 7-hydroxymitragynine were given orally for 5 days [51]. In terms of analgesic activity, mitragynine is around 13 times more effective than morphine while 7-hydroxymitragynine is four times more effective than mitragynine [36,51]. Alkaloids in kratom can interact with opioid and monoaminergic receptors but they differ from opioids in structure [52]. Mitragynine is an agonist of multiple receptors that binds not only μ - and κ -opioid receptors, but also additional receptors that might augment its effectiveness at mitigating opioid withdrawal [53,54]. Kratom's opioid-like effects at lower doses may be comparable to morphine's equivalent effect at lower doses [30]. Effects are dose dependent, beginning 5–10 min after using, and continuing for 1 h after exposure [46]. In addition, a variety of chemicals separated from kratom have been shown to present opioid-like activity on smooth muscle systems and in ligand-binding studies [35,37,55]. Most distinctly, many regions of the central nervous system are sensible to the external effects of these kratom originated substances and the effects can be interfered by opioid antagonists [35,37,41,51,55–57].

3.2.3. Toxicology

Although the use of kratom is increasing, scientific research of its adverse effects and toxicity is still scarce. As mentioned above, the pharmacologic effects of kratom leaves and their constituents are dose-dependent. Low to moderate dosages (1–5 g) can offer light stimulant effects to help workers against fatigue, and moderate to high dosages (5–15 g) may have opioid-like effects [36]. Therefore, kratom can be used for controlling pain, diarrhea, and opioid withdrawal symptoms [32,46,50,58,59]. But kratom also has stimulant effects at high dosages (>15 g) [42,46,60]. Some individuals may have anxiety, irritability, and enhanced aggression due to stimulant effects, and long-term, high-dose consumption has been related to several atypical effects [36]. Hyperpigmentation of the cheeks, tremor, anorexia, weight loss, and psychosis have been noted in individuals with long-term addiction [46].

In the past 5 years, there are nine fatal cases of intoxication associated with the use of kratom-based product known as “Krypton”, a mixture of mitragynine and *O*-desmethyltramadol [61,62]. However, the mortalities have been ascribed to the addition of *O*-desmethyltramadol to the dried kratom leaves [61]. Thus, it can be concluded that the use of kratom is not negligible, more clinical, pharmacological, socio-anthropological, and toxicological studies are needed to tackle this marginally explored issue [63].

3.3. *S. divinorum*

Salvia (*S. divinorum*, Lamiaceae) is a perennial herb native to Oaxaca, Mexico. Traditionally it was used by the Mazatec

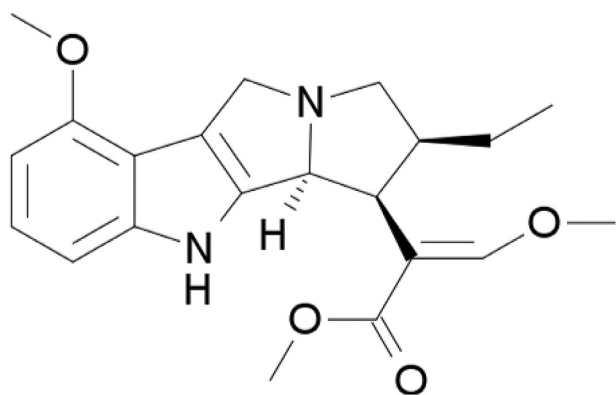


Fig. 3 – Chemical structure of mitragynine.

Indians for religious practices and medical purposes, although there is no approved medicinal use for *S. divinorum* or its active ingredient salvinorin A. Its street names include “Psychedelic Sage,” “Diviner’s Sage,” “Mystic Sage,” “Salvia,” “Sally-D”, and “Magic Mint” etc. In 2009, UN Member States identified *S. divinorum* as the most common plant-based NPS, and in 2012 it was the third, after khat and kratom. The active component for psychoactive effects of *S. divinorum* is salvinorin A, which is a diterpene, the first non-alkaloidal hallucinogen. The concentrations in the leaves of *S. divinorum* depend on the growing conditions and preparation procedures. *S. divinorum* is usually sold as seeds or leaves, but a combination of dried leaves and extracts of salvinorin A is also available in the market [35]. *S. divinorum* is also one of the most widely marketed recreational plants available through the Internet [64]. Many advertisements on websites mentioned it as a “legal” hallucinogen to promote experimentation with a combination of dried leaves and extracts of salvinorin A as “the freshman selection” or the “starter pack” [65]. Traditional consumption of *S. divinorum* is via sucking and chewing the fresh leaves or alternatively grinding the fresh leaves to make a drinkable liquid. Many users self-reported to inhale vaporized salvinorin A extract, or smoke the dried leaves to have short but strong hallucinations.

While there are more than 500 species of salvia, *S. divinorum* has been identified for its hallucinogenic characteristic for centuries. Both adults and adolescents internationally regard *S. divinorum* as a recreational substance. In a latest research of innovative adolescent drug users, 25% of the investigated adolescents expressed they obtained information about *S. divinorum* via the Internet [66]. Although *S. divinorum* and salvinorin A are not controlled by any international conventions so far, they are increasingly controlled due to the growing use in some countries [35].

3.3.1. Chemistry

Salvinorin A (Fig. 4) is unique from other naturally occurring hallucinogens since it is not an alkaloid but a neo-clerodane diterpene. Although there are several structurally related salvinorins found in the *S. divinorum* plant, it seems to be the only active naturally occurring salvinorin.

3.3.2. Pharmacology

Salvinorin A is a potent and highly selective agonist of the kappa opioid receptor (KOR) that is present in the spinal cord and brain [67]. Studies on the structure–activity relationship of salvinorin A with KOR have shown that the potency and duration of action can be increased if its structure is modified at C-2 (Fig. 4) [67–70]. Transformation of other compounds at C-2 can also extensively affect functional selectivity at the μ (μ) opioid receptor (μ -OR) [71]. In contrast, while small substituent at C-16 has hardly any effect, transformations at other positions, such as C-1 ketone, C-8 epimer, C-12 furan, and C-17 lactone, result in substantial reduction or elimination of affinity for opioid receptors [67, 70]. The affinity for κ -OR is significantly reduced by most transformations of the furan ring [67, 70].

Psychotomimesis, diuresis and spinal analgesia can be induced by stimulation of the kappa-receptor, but without respiratory depression. Results of the research on the

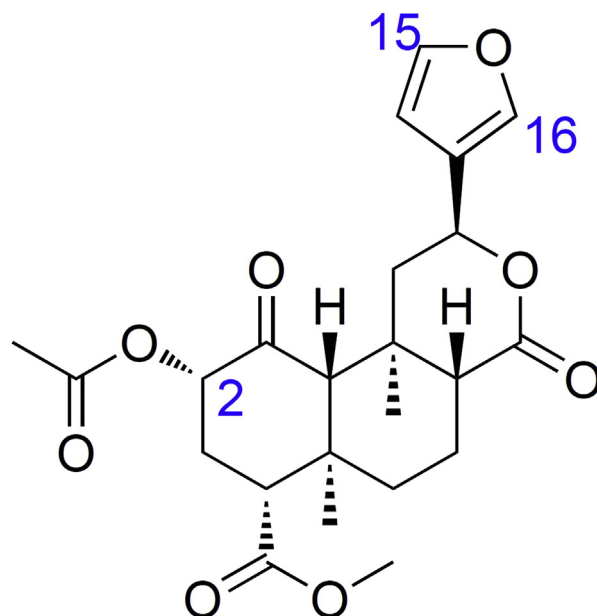


Fig. 4 – Chemical structure of salvinorin A.

pharmacological activity of salvinorin A are consistent with the effects of KOR agonists such as analgesia, sedation, inhibition of GI transit, and depressant effects [72–77]. The mechanism on how KOR agonists initiate hallucinations is unknown, but a role in perception disorders, including schizophrenia and depression, has been proposed [78]. *S. divinorum* could be used as a probe to verify the molecular basis of psychiatric conditions due to selectivity of salvinorin A for the KOR [79]. Salvinorin A is absorbed rapidly via the buccal mucosa; both extract and leaf forms can produce psychoactive effects within seconds to minutes, and last for up to 1 h. Inhalation can induce psychoactive effects within seconds, which last up to 20–30 min. Threshold dosages of *S. divinorum* to produce hallucinations vary with the routes of administration [80]. The threshold dosage of salvinorin A by inhalation is 200 mg for hallucinations, while 10 mg fails to induce hallucinations. Studies of salvinorin A absorption via the intravenous administration are lacking in humans but have been performed in animal models [81]. There are three subsets of the hallucinogens, including psychedelics, dissociative, and deliriant. Salvinorin A has been classified into the dissociative, in pace with phencyclidine (PCP, angel dust), ketamine, dextromethorphan, ibogaine, and nitrous oxide [81].

3.3.3. Toxicology

S. divinorum has been indicated with low toxicity and low addictive potential from animal studies [82]. Comparing with other hallucinogens, especially amphetamine derivatives such as MDMA, salvinorin A has rarely been reported for its toxicity [83]. There are limited studies that reports about acute or chronic toxicity associated with *S. divinorum* in humans, but psychosis in vulnerable individuals has been observed in clinic. So far, there are no fatality case reports due to use of *S. divinorum*.

3.4. Hallucinogenic (or magic) mushrooms

Hallucinogenic mushrooms, also called “magic mushrooms”, are the psychotropic fungus containing psilocybin and psilocin (Fig. 5) [84]. They have a huge difference in potency depending on the sorts or species of use, place of origin, growing conditions, and age. At low dosage, the main effects of magic mushrooms are perceptual distortions and changes of thought or mood. The majority of them are sold by heads or smart shops in the Netherlands, and the consumption and possession of magic mushrooms have become illegal as List II in the Dutch Narcotic Law along with cannabis since 2008.

Although their names consist of “hallucinogenic”, hallucination occurs rarely after using them. They are categorized into three major subsets based on their chemical structures, including indolealkylamines or tryptamines (e.g. psilocybin and psilocin), phenethylamines such as mescaline and methylenedioxymethamphetamine (MDMA) [84].

3.4.1. Chemistry

Psilocybe cubensis and *Psilocybe semilanceata* (or “psilocybe”) that are commonly known as “liberty caps” contain 10 mg psilocybin per gram of dried mushroom weight (1% w/w). Some species like *Psilocybe bohemica* contain a little more psilocybin. The average dosage of psilocybin could induce hallucinogenic effects is 4–10 mg [85] or 50–300 g/kg body

weight [86]. Therefore, the minimum dosage to get the desired recreational effect is around 1 g of dried magic mushrooms or 10 g of fresh magic mushrooms. Interestingly, psilocin and psilocybin, the psychoactive substances, are more stable in dried mushrooms than in fresh ones. However, following 4 weeks storage of the fresh magic mushrooms, the Netherlands Food and Consumer Product Safety Authority could only find traces of psilocin and psilocybin [87].

Psilocybin is converted into the pharmacologically active compound psilocin in the body by a dephosphorylation reaction through alkaline phosphatases. Psilocybin is a tryptamine derivative, and is structurally similar to the neurotransmitter serotonin. Phenylethylamine, a sympathomimetic amine structurally related to amphetamines, was also found in some mushrooms [85], and might induce the cardiovascular effects like tachycardia and other adverse reactions such as nausea and anxiety.

3.4.2. Pharmacology

The major adverse effects of magic mushrooms are associated with the central nervous system and sympathomimetic effects vary greatly between individuals and the duration time of use [88]. People may have the feelings of relaxation, dizziness, euphoria, visual disturbances, delusions, illusion, or real hallucinations. Other adverse effects include restlessness, incoordination, anxiety, and faint judgments of time or distance etc. but in general, body temperature remains normal. Users may use ‘bad trips’ to describe their panic reactions and psychosis-like states. However, apparent physical symptoms have been recorded such as severe stomach pain, persistent vomiting, and diarrhea [84].

3.4.3. Toxicology

The physiological side effects, such as nausea, vomiting, trepidation, abdominal pain and dilation of pupils (mydriasis), were often observed after consumption of magic mushrooms, and the common finding of intoxication was tachycardia [89]. At an oral dose of 0.2 mg/kg psilocybin, mild-to-moderate increase in breathing frequency, heart rate, and systolic and diastolic blood pressure (+25, and +10 mm Hg, respectively) was reported [88, 89]. The temporary increase in blood pressure may be a risk factor for users’ cardiovascular conditions, especially hypertension without any treatments [86].

The duration of a ‘trip’ usually lasts 2–6 h. Moderate adverse effects such as sleep problems may persist up to 12 h. In 2004, there were high rates of anxiety (32%) and paranoia (35%) among 174 magic mushroom users reported in a UK survey [90]. Recently, with a web-based survey, magic mushrooms were regarded as benefits with low harm potential among hallucinogenic drug users [91].

3.5. Mandrake

Mandrake is the general name for any herbal, perennial plants included in the genus *Mandragora* [90]. The most well-known mandrake is *Mandragora officinarum* [92]. Mandrake is native to the eastern Mediterranean region and distributed in southern Europe, the Middle East and northern Africa, and

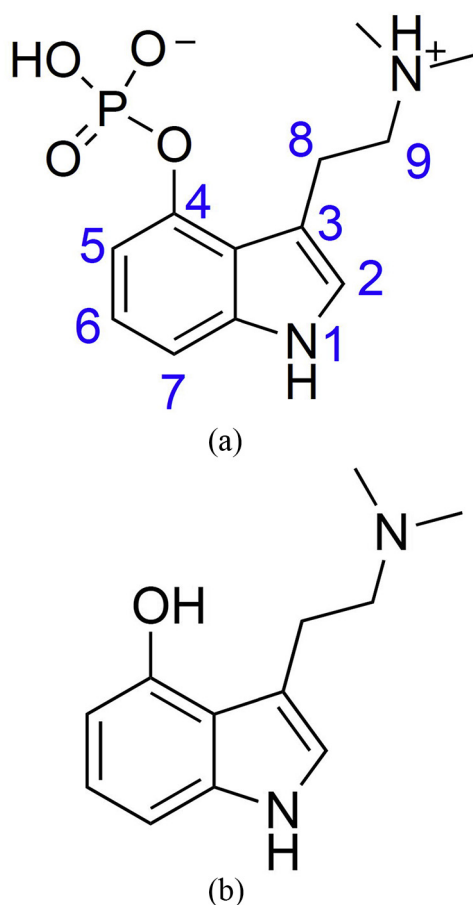


Fig. 5 – Chemical structures of (a) psilocybin (b) psilocin.

also Himalayas [92]. The name was Latinized from two Sanskrit words: 'Mandros' (sleep) and 'Agora' (substance), meaning 'sleep producing drug'. The word "mandrake" is also used frequently for plants' roots with poisonous alkaloids. Mandrake is known for its aphrodisiac, healing, hallucinogenic, and poisonous characteristics. Its fruits are also called love apples that were thought to increase fertility [90].

3.5.1. Chemistry

In ancient times, mandrake had been used as an anodyne and a sedative to anesthetize patients during surgery, but an overdose can be fatal. All parts of mandrake contain active alkaloids, especially in fresh and dried mandrake root. Mandrake contains 0.3–4.0% tropane-based alkaloids, such as atropine, hyoscyamine (daturnine), and scopolamine (hyoscine). Tropane alkaloids make the root and leaves poisonous via anticholinergic, hallucinogenic, and hypnotic effects. In the Solanaceae family, the concentration of tropane alkaloids is not as high as some other plants, but if a person had high mandrake consumption or had an allergic reaction, fatality could occur [92–94].

Atropine i.e. ($\pm$)-hyoscyamine, obtained from deadly nightshade is a poisonous crystalline alkaloid. It can inhibit the autonomic nervous system, speed a slow heart rate, relieve spasms, decrease secretions, exert anticholinergic effects, and is used to dilate the pupil of the eye locally [94–96].

Scopolamine (also called hyoscine, Fig. 6a) is a colorless, water-soluble alkaloidal poison. The primary use is as a sedative and mydriatic to prevent the symptoms of motion disease; it is also taken as an anticholinergic and sedative. (–)-Hyoscyamine (Fig. 6b) is a poison obtained from henbane and other Solanaceous plants. It is a white crystalline alkaloid, and used as a sedative, analgesic, mydriatic, and antispasmodic. Relative to atropine, (–)-hyoscyamine has similar uses but more potent effects [92].

3.5.2. Pharmacology

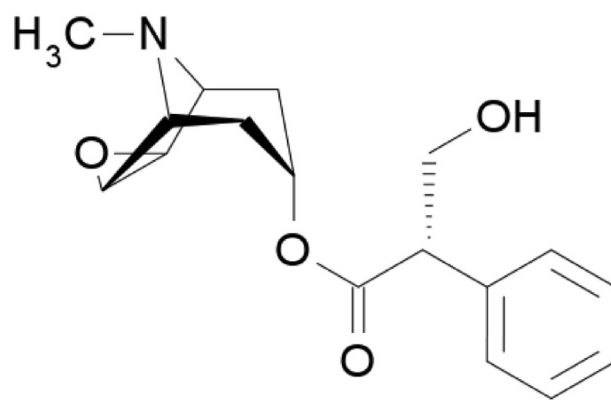
Mandrake has been well known as anticholinergic, therefore it could restrain the neurological signals transmitted by the endogenous neurotransmitter, acetylcholine. But there are adverse effects including mouth dryness, ataxia, urinary retention, hallucinations, coma, and even death.

Tropane alkaloids, esters of the tropines with various acids, have been used for their sedative, analgesic, antispasmodic and mydriatic effects. Hyoscyamine and atropine in comparatively high doses could cause central effects from stimulation of the cerebrum, midbrain and medulla oblongata, leading to coma and depression [95]. Hyoscine is the other active principle of mandragoras to affect the memory and cause predominantly central respiratory depression in high doses [96,97].

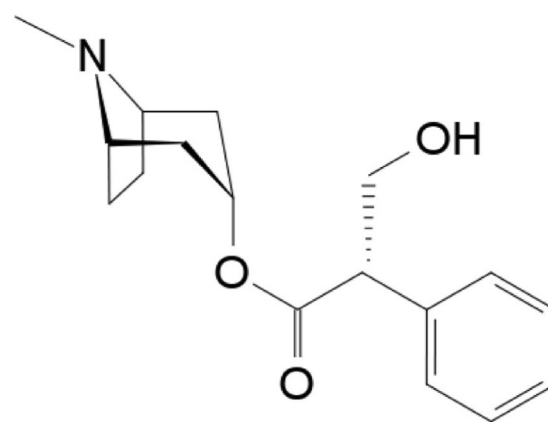
3.5.3. Toxicology

Mandrake's medicinal uses can date back to ancient times. Before surgery, it was given to patients by chewing pieces of root. The root is toxic, but also can be used as a painkiller to relieve and alleviate pain for its soporific characteristics. It has been used to induce vomiting and bowel movements [98].

The effects of mandrake consumption include severe symptoms similar to atropine poisoning, such as blurred



(a) Scopolamine



(b) Hyoscyamine

Fig. 6 – Chemical Structures of (a) scopolamine (b) hyoscyamine.

vision, mydriasis, and dryness of the mouth, difficulty in urinating, dizziness, vomiting, and tachycardia. The majority of patients also have hyperactivity and hallucination [99].

4. Conclusion

This work reviewed plant-based substances of NPS that have recently emerged on the recreational drugs market. As mentioned above, there were numerous NPS or so-called 'designer drugs' used in non-medical purposes to be synthetic alternatives for illicit drugs of abuse [100]. NPS are easily available, and would not be detected by standard screening tests so far [88]. And because the structures of NPS can be chemically modified easily to alter its properties, the items of new synthetic NPS can be expected to increase very quickly.

The Natural NPS, which are often the origin of synthetic NPS, therefore deserve further scrutiny. In this review, khat, kratom, salvia, magic mushroom and mandrake are all easily available to general public. Some of them have been consumed as traditional medicines or ritual substances but their abuse or addictive potentials are not fully elucidated. In addition, their adverse effects could even be fatal if improperly consumed.

Thus, it is deemed necessary to develop a standard and sensitive screening mechanism to early detect NPS for the purposes of prevention, policy-making and regulation.

Conflict of interests

The authors declare no conflict of interests.

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