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750 *Current Neuropharmacology*, **2017**, *15*, 750-761

REVIEW ARTICLE

Herbal Highs: Review on Psychoactive Effects and Neuropharmacology

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ARTICLE HISTORY

Received: May 05, 2016
Revised: June 12, 2016
Accepted: October 03, 2016

DOI:
10.2174/1570159X14666161031144427

Abstract: ***Background*:** A new trend among users of new psychoactive substances' the consumption of "herbal highs": plant parts containing psychoactive substances. Most of the substances extracted from herbs, in old centuries were at the centre of religious ceremonies of ancient civilizations. Currently, these herbal products are mainly sold by internet web sites and easily obtained since some of them have no legal restriction.

***Objective*:** We reviewed psychoactive effects and neuropharmacology of the most used "herbal highs" with characterized active principles, with studies reporting mechanisms of action, pharmacological and subjective effects, eventual secondary effects including intoxications and/or fatalities

***Method*:** The PubMed database was searched using the following key.words: herbal highs, *Argyreia nervosa, Ipomoea violacea and Rivea corymbosa; Catha edulis; Datura stramonium; Piper methysticum; Mitragyna speciosa.*

***Results*:** Psychoactive plants here reviewed have been known and used from ancient times, even if for some of them limited information still exist regarding subjective and neuropharmacological effects and consequent eventual toxicity when plants are used alone or in combination with "classical" drugs of abuse.

***Conclusion*:** Some "herbal highs" should be classified as harmful drugs since chronic administration has been linked with addiction and cognitive impairment; for some others taking into consideration only the recent trends of abuse, studies investigating these aspects are lacking.

Keywords: Herbal highs, plant material, psychoactive herbal products, neuropharmacology.

INTRODUCTION

Among New Psychoactive Substances (NPS), a new trend among users includes the consumption of "herbal highs": plant parts containing psychoactive substances [1]. These herbal products, mainly coming from South America or Asia where this material has traditionally been used since ancient times, recently increased their popularity. The possibility of e-commerce, the popularity through web forum of users opened the market to this "natural" (opposite to synthetic) option to consume psychoactive compounds. Unfortunately, at the moment there are no data about the number of persons consuming herbal highs nor about relevance of consumption on the online market or in dark market just because information, diffusion and selling are made anonymously, by web forums and as mentioned earlier mainly by dark internet. What is known by the most recent global drug survey is that one out of 10 survey participants used "dark net" to buy NPS including herbal highs, that 5% respondents did not use any NPS before knowing and using this drug supply system and finally that even if classical drugs of abuse consumption is still highly prevalent, some "herbal highs" use (*e.g.* Kratom or khat) in the last year was reported by about 1% responders [2].

Most of the "herbal highs" have been well known in the past centuries and used as sacred substances in traditional rites or as medicines by different ancient cultures [3]. Actually herbal highs are perceived as safe products since, as above reported, they are "natural" and "biologic".

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1570-159X/17 $58.00+.00

Nevertheless, similarly to many synthetic drugs, plant and herbal supplements used recreationally can show a broad spectrum of euphoric, stimulant, and mainly hallucinogenic effects. Even if abuse liability is not a crucial point for these products, serious adverse effects can occur after consumption, due also to the false perception that these products are safe, legal, and organic.

Currently, an established definition of herbal highs does not exist. In the majority of cases this is intended as a synonymous of "legal highs", which is not. Conversely, the pharmacological identity of legal highs often resembles substances legally controlled (*i.e*. amphetamines, cannabis). However legal highs can be legally consumed and obtained from online vendors or in so-called "head shops" [4].

Nor herbal highs can be considered as "spice drugs" defined as herbal blends containing synthetic cannabinoids surreptitiously added to obtain psychotropic effects [5]. The plant can contains one or more active component that, *per se*, undergoes to drug law policy. However, it can occur that the plant or part of it are not included, and can be considered legal. There are several web sites where it is possible obtain herbal products anonymously and with a very low control level.

In this review, as" herbal highs" we considered those plants or part of them containing psychoactive active principles (alkaloids, terpenes, *etc*), which are used as fresh or dry material to be chewed, smoked, drunk as a tea, or as a juice or beverage in the aim of obtaining psychotropic effects.

Among the elevated number of vegetal material with the above reported characteristics, we chose to review not only the ones with characterized active principles, with studies reporting mechanisms of action, pharmacological and subjective effects, eventual secondary effects including intoxications and/or fatalities, but also those which acquired more interest among users and result, by anecdotal information, the most used.

Specifically, we focused on the psychoactive effects and neuropharmacology of: *Ayahuasca; Argyreia nervosa, Ipomea violacea* and *Rivea corymbosa, Catha edulis, Datura stramonium, Piper methysticum, Mitragyna speciosa,* Hallucinogenic cacti from *Trichocereus* family, *Salvia divinorum* and *Tabernanthe iboga*.

METHODS/LITERATURE SEARCH STRATEGY

Relevant scientific articles were searched from Medline, Cochrane Central, Scopus, Web of Science, Science Direct, EMBASE and Google Scholar, up to March 2016 using the following keywords: herbal highs, *Ayahuasca; Argyreia nervosa, Ipomea violacea* and *Rivea corymbosa; Catha edulis; Datura stramonium; Piper methysticum; Mitragyna speciosa; Trichocereus* cacti; *Salvia divinorum* and *Tabernanthe iboga* and the known active principles of the above reported plants plus pharmacology, neuro-pharmacology and psychoactive effects. Then, the references of each found article were revised to find other information relative to the searched plant.

RESULTS

Ayahuasca: the Magic Drink Made of *Banisteriopsis caapi* and *Psychotria viridis*

Ayahuasca (aka, Huasca, Yagé, Daime, Pharma-huasca, The Vine, The Tea, La Purga, vine of the souls) is a powerfully psychedelic South American brew, traditionally made from *Banisteriopsis caapi* hallucinogenic vine in the Malpighiaceae plant family (which contains β-carboline harmala alkaloids: harmine, harmaline and tetrahydroharmine) along other medicinal plants, *i.e*. *Psychotria viridis* containing the hallucinogenic active principle dimethyltryptamine (DMT) [6]. Even if the above reported plants are most commonly used to prepare the beverage, *Mimosa hostilis*, *Mimosa tenuiflora Anadenanthera peregrina*: *Pilocarpus organensis*, *Acacia obtusifolia* are also employed as a font of DMT whereas *Peganum Harmala* and *Passiflora* or *Passion flowers* as font of harmala alkaloids [6].

In the ancient times, the shamans of the indigenous western Amazonian tribes usually took the plant as purgative and/or antiparasitic during the religious and healing ceremonies, while presently it is a sacred beverage of some religious communities in Brazil and North America (Santo Daime) [7].

Ayahuasca is usually prepared by boiling or soaking parts of the above reported plants [6]. During the process, DMT, which is practically inactive if orally taken, as it is broken down by the digestive enzyme monoamine oxidases (MAOs) before reaching the central nervous system, became active and effective when combined with a β-carbolines contained in *Banisteriopsis caapi*, which are potent MAOs inhibitors [8].

Psychedelic effects of *Ayahuasca* are dose-dependent. Their onset takes generally 20-60 minutes after oral intake and may last approximately 2-6 hours. They may comprise vomiting and/or diarrhoea (which usually accompany the 'psychedelic experience'), strong visual effects (*e.g*., snakes, big cats, insectoid aliens, *etc*.), euphoria, mind-altering entheogenic effects [9]. Conversely adverse effects include untoward effects include fear, paranoia, disequilibrium, coma up to death [10].

Although the endogenous presence of DMT in brain tissue is recognized, its biological function remains a mystery [11]. It has been hypothesized that DMT may have a role, not yet been established, in normal physiology and/or psychopathology [11]. At central nervous system receptor level, DMT interacts with serotonergic neurotransmission due to its structural similarity with the endogenous neurotransmitter serotonin (5-hydroxytryptamine; 5-HT) Furthermore, DMT is an agonist for 5-HT2A and 5-HT1A receptors sites [12]. Furthermore, similar to the classical psychedelics, *i.e*, mescaline, LSD, psilocybin, DMT presents agonist activity for the 5-HT2Areceptor [12]. It has been shown that psychedelic 5-HT2 agonists stimulate the expression of genes encoding transcription factors, such as egr-1 and egr-2 [13]. These transcription factors have been implicated in synaptic plasticity and in some aspects of reasoning, such as memory and attention [14-16]. DMT also interacts with the intracellular sigma-1 receptor promoting neural plasticity

through dendritic spine formation, trace amine associated receptor and vesicle monoamine and serotonin transporters [17-19].

It has been postulated that whereas DMT action on 5-HT2 receptors is responsible for acute effects induced by *Ayahuasca*, changes in transcription factors may affect changes in personality observed in long-term users of *Ayahuasca* [20]. It was shown that repeated exposure to *Ayahuasca* could cause structural differences in the posterior cingulate cortex, and consequently a shift in attitudes and interests towards less materialistic values and superior open-mindedness. It is also plausible that the antidepressant effects recently reported for *Ayahuasca* are partly mediated by agonism on sigma-1 receptor, an effected shared with some selective serotonin reuptake inhibitors, such as fluvoxamine [21]. Finally, *Ayahuasca* subjective effects are also due to the pharmacological actins of the β-carbolines, contained in *Banisteriopsis caapi*. These substances not only inhibit MAOs enzymes, but also act as the inhibitors of the serotonin transporter [22].

Argyreia nervosa, Ipomea violacea and *Rivea corymbosa*: The Plants with Hallucinogenic Seeds

Argyreia nervosa (also called Hawaiian Baby Woodrose, Adhoguda or Vidhara, Elephant Creeper and Woolly Morning Glory) is a perennial climbing vine with pink flowers, native to the Indian subcontinent and introduced to numerous areas worldwide, including, Africa, Subtropical America, and Europe. The two botanical varieties are *Nervosa* and *Speciosa*; for both, the whole plant has been used in traditional ayurvedic medicine [23]. Leaves of the plant have antibacterial and antimicrobial activity, roots are used in rheumatism, gonorrhea, chronic ulcer and diseases of nervous system. The plant is also used as a tonic, diuretic and aphrodisiac, and has been shown to have hypoglycemic, immunomodulatory, hepatoprotective, anti-inflammatory, and analgesic activities [24, 25].

Ipomoea violacea (Morning glory, Heavenly blue, Pearly Gates, Flying Saucers, Blue Star, Wedding Bells, Summer Skies, or Badoh negro) with purple flowers is also perennial climbing vine coming from South America. It has been described that the plant seeds (named ololiuqui and tlitliltzin) have been used in divinatory ceremonies because of their hallucinogenic properties by the native Americans [26].

Rivea corymbosa (Christmasvine, Christmaspops, and snakeplant) is a perennial climbing vine too with white flowers, native throughout Latin America from Mexico as far south as Peru and widely naturalized elsewhere. The plant has been used both in the traditional medicine and in religious rituals with respect to the hallucinogenic mushrooms like the peyote [26].

Indeed, the divinatory hallucinogenic properties of these three climbing vines are due to psychoactive alkaloids exclusively present in the plants seeds. The principal psychoactive alkaloids identified in the seeds are ergine (lysergamide, lysergic acid amide, LSA) and isoergine, compounds able to induce psychoactive effects like those from lysergic acid diethylammide (LSD), but with fewer intensity [27, 28].

Whereas the seeds of *Argyreia nervosa* contain about 0.14% (dry weight) of ergine and 0.19% isoergine alkaloids, those of Ipomea violacea 0.2% (dry weight), while *Rivea corymbosa* seeds a percentage of alkaloids between 0.02 and 0.06% [28-31]. Lysergic acid alkaloids were previously isolated only from mushrooms of the Claviceps, Penicillium or Rhizopus family [32, 33]. It has been shown that a 2 to 5 mg dose of ergine is requested for the hallucinogenic action [32, 33]. The alkaloid seems to inhibit adenylate cyclase and reduce cyclic adenosine monophosphate formation by activating the dopamine receptors D2 [34]. LSA has psychomimetic effects (mind alterations, hallucinatory perceptions and state of awareness) similar but 50-100 times less powerful to LSD, that persist for about 4-8 hours. The ingestion of seeds could lead to serious psychotic adverse effects, like dissociative reactions and schizophrenic relapses. The literature has described some cases of toxic psychosis characterized by hallucinations, orientation problems, anxiety, and psychomotor agitation after the ingestion of *Argyreia nervosa* seeds [35, 36].

A recent study highlighted the variable adverse effects in subjects after ingestion of equal doses of *Argyreia nervosa* seeds with interindividually highly differing reactions in type and intensity. The study concluded that fluctuating alkaloid contents in seeds and multi-drug intoxications make the use of this legal high far more dangerous than commonly believed [37].

Catha edulis: The Psychostimulant Khat

Catha edulis is an evergreen shrub cultivated in East Africa and in South-West Arabian Peninsula. It is commonly called khat, qat or chat [38]. The principal psychoactive components of khat are cathinone and cathine. Cathinone, ((-)-2-aminopropiophenone) is a chemically labile compound and in a short time after khat leaves harvesting it is transformed to the non-pharmacologically active 3,6-dimethyl-2,5-diphenylpyrazine. It is for this reason that khat needs to be consumed while still fresh. During maturation, cathinone is enzymatically converted to cathine (1S, 2S-norpseudoephedrine), The two substances are chemically and pharmacologically related to amphetamines and more in general to phenetilamines. In this concern, it's worth of notice to mention that two-thirds of new "designer drugs" reported by the Global Drug Survey were represented by synthetic cathinones, cathinone structural analogues [2].

Similarly to amphetamine, cathinone-induced psycho-stimulation is mediated primarily *via* the meso-striato–cortico limbic dopaminergic pathway [39]. Furthermore, cathinone was shown to inhibit the re-uptake of epinephrine, norepinephrine, and serotonin in animal models [39]. However, like in case of domaminergic stimulation, cathinone is a threefold less potent than amphetamine in causing serotonin release [40]. Although the psychostimulatory effects of khat appear to be completely explained by the action of cathinone, other plants alkaloids are likely to contribute to plant effects. Indeed, at peripheral level cathine shows the same simphathomimetic effects as cathinone, even if its action on central nervous system appears negligible because of its less lipophilic properties [41].

The recreational effects of khat are commonly obtained by chewing the fresh vegetable plant parts (stems, leaves and flower buds), although khat can be also ingested as an infusion or smoked. Typically, 100–200 g of khat leaves wrapped as a bundle in banana leaves are consumed in a session, and its effects last for several hours [42]. Khat chewing is a traditional habit in eastern Africa and Arabian peninsula, but the influx of immigrants from these countries has resulted in the importation of khat to countries where these immigrants have settled, including Europe and the United States [43]. Moreover, several internet websites sell and ship fresh khat leaves everywhere [44]. Differently from other consumers of psychoactive substances and "legal" or "herbal highs", khat users are unlikely to use other psychoactive substances [45].

When chewing khat, cathinone is released producing a feeling of euphoria [46]. Cathinone also reduces appetite through an unknown mechanism [47]; other effects include increased blood pressure associated with a rise in the occurrence of vasospasms, acute myocardial infarction, unfavorable cardiovascular effects and also problems related to the gastrointestinal tract: esophagitis, gastritis [48]. Many cases of acute liver failure and many cases of autoimmune hepatitis among consumers of *Catha edulis* have also been reported [49].

The fact that in recent decades the traditional habit of chewing khat leaves changed towards uncontrolled consumption generated a number of reports of psychiatric disorders following plant use. Different forms of psychosis, hallucination, depression and personality disorders have been associated with long-term khat use [50].

In reality, as in case of other psychotropic drugs, khat is likely to exacerbate pre-existing psychological disorders, or it is used by individuals vulnerable to overcome stress caused by the same disorders [50]. The characteristics of psychoses following khat use are very similar to those seen in chronic amphetamine and cocaine addicts [51].

There have been reports of khat-induced aggressive verbal outbursts and violent behaviour in the past, and also a recent work describes the presence of disruptive and violent behaviour amongst chronic khat users [52, 53].

Datura stramonium: The Devil Weed

Datura stramonium (aka, Jimson Weed, Angel's trumpet, moon flower, Thorn Apple, Estramonio, Dhaturo, Madak, Mad Apple, Trompetilla) is a wild-growing hallucinogenic plant belonging to the Solanaceae family [54]. *Datura stramonium* contains a mixture of anticholinergic alkaloids, *e.g*. atropine, hyoscyamine and scopolamine ((-) hyoscine) which are the main responsible of its neurotoxic and hallucinogenic effects [55]. It widely grows as "*gegemu*" among the Yorubas in the south-western Nigeria, where it is mainly used as source of medicines, intoxicants, dyes and poison [56]. It is also widely cultivated in Europe, Asia, America and South Africa. Traditionally, it has been used for mystic and religious purposes and in Ayurvedic medicine as an herbal medicine with narcotic effects and to relief asthma/bronchitis, flu symptoms, headache, rheumatism, haemorrhoid, gout and pain and as sedative in hysterical and psychotic patients and in the treatment of insomnia [57]. However, as *Datura* owns a narrow range between the active and lethal dose, it has been widely documented its accidental poisoning, particularly in contaminated food [58].

Recently, orally and smoked recreationally abuse/misuse of *Datura* leaves or flowers or the seeds has been reported by youngsters in search of strong sensations and to experience their hallucinogenic effects [59]. Among the most commonly reported desired effects, euphoria, surreal interactions with world and auditory hallucinations have been frequently reported by recreational users. After oral intake, the effects may arise in around 20-30 minutes, depending on the dose; whilst if smoked, the effects are faster (around 5 minutes). After the intake of moderate doses, the effects last approximately 8-12 hours; while higher doses may also last 2-3 days.

Datura seeds and flowers are usually more potent than the leaves and roots. Scopolamine and atropine are anticholinergic hallucinogens which competitively act by inhibiting acetylcholine at muscarinic receptors, which in turn excite dopaminergic neurons at the peripheral level of the parasympathetic nervous system and at the central nervous system level. Parasympaticolytic effects include :1) spasmolytic effect (bronchial smooth musculature); 2) midriasis and paralysis of the visual accommodation; 3) decrease of the secretory activity of the exocrine glands; 4) tachycardia; 5) suppression of nausea and vomiting [60].

Several cases of toxicity following voluntary and recreationally ingestion of *Datura* extract were reported, particularly among children and teenagers [59, 61, 62]. The main clinical effects include anticholinergic delirium, restlessness, altered sensorium disorientation and a wide range of hallucinations (colloquially defined as Toxidrome: "Blind as a bat, mad as a hatter, red as a beet, hot as a hare, dry as a bone, the bowel and bladder lose their tone, and the heart runs alone") [54, 62]. At higher doses, it may cause incoherent speech, disorientation, delusions, dreamlike frenzy, often followed by depression and amnesia; in some cases, a sudden surge in strength, energy and subsequent aggressive compulsions [59]. Deep coma and convulsions may occur as well [62]. Moreover, peripheral nervous system symptoms may appear, including mydriasis, dry skin and mouth, urinary retention, blurred vision, inability to perspire, hyperpyrexia and constipation [54].

Long-term consumption of Datura (around 3 to 4 seeds throughout the day with a maximum intake of 6 seeds/day over a period of 3 years) resulted in the onset of paranoid schizophrenia, an altered state of consciousness and aggressive behaviour [63]. Finally, even fatalities related to the intake of *Datura stramonium* were reported, mainly due to its accident consumption [64-66].

Piper methysticum: The Kava-kava Nature's Legal Relaxant

Kava-kava (or Sakau or Kawa Kawa, ava root, awa, cavain, gea, gi) is the name given to a typical beverage prepared with *Piper methysticum*, a plant belonging to the black pepper family, originating from Melanesia and then rooted in the Polinesian islands [67]. The roots of the plant

are rich of kavain, the principal active ingredient and they have been used since at least 3000 years ago in preparing kava-kava, that could be considered the "national drink" of Polynesia and Melanesia. In the past kava-kava played an important role in different religious and political ceremonies, and still today it is consumed to restore the physical resistance, help sexual performances, acts as an aphrodisiac, alleviate stomach pain and many other indispositions.

In some western societies, kava-kava is used as a prescription-free alternative to the benzodiazepines to relieve stress-induced anxiety and insomnia [68]. If taken in little doses, kava-kava produces a sensation of wellbeing, sharpens the intellectual faculties and makes difficulties easier to take. When it is used at medium doses, it acts as a muscular relaxant and as spasmolytic producing a quiet and pacifying sleep, rich in pleasant dreams. High doses lead a deep sleep [69, 70].

The clinical effects of kava-kava are related to a group of structurally-related, lipophilic compounds known as kavalactones (or kavapyrones), with kavain representing the most important one [71, 72]. Numerous proteins including γ-aminobutyric acid type A receptors (GABAARs), voltage-gated N^{a+} and Ca^{2+} channels, opioid μ and δ receptors, dopamine type-2 receptor, histamine type-1 and 2 receptors, cannabinoid type-1 receptor, and monoamine oxidase type B have been suggested to be the molecular targets for kavalactones [71, 73]. Recently, kavain was found to affect the expression of TNF-α, an endogenous factor induced by inflammatory stimuli although the molecular basis for that regulation remains unclear [74, 75].

Facial turgidity, hematuria, macrocitic anaemia, ataxia, increased patellar reflexes, weight and hair loss, cutaneous eruptions, dyspnea, vision problems, hepatotoxicity, gastrointestinal troubles, allergic cutaneous reactions, headache, photosensitivity, asthenia, agitation, drowsiness and tremors have been associated with chronic consumption of *Piper mesthycum* in high doses [76, 77]. Numerous reports of severe hepatotoxicity potentially induced by kava-kava have also been highlighted, both in the USA and Europe [49].

Kava-kava effects can be improved by the assumption of other substances acting on the central nervous system, like alcohol and certain medicaments, leading to a temporary reduction of the cognitive performance or to a partial loss of conscience. On the other side, *Piper methysticum* can interact with the metabolism of numerous drugs by inhibiting certain isoforms of cytochromes P450, leading to higher risk of side effects [78, 79]. Recently it has been described a case of suicide due to overdose of kavalactones using intravenous. injection together with administration of ethanol [80].

Mitragyna speciosa: The Psychedelic Kratom

Mitragyna speciosa (Kratom) is an original tree belonging to the Rubiaceae family (*i.e.* coffe plant) of South-East Asia, where the plant is used in folk medicine as a stimulant (at low doses), sedative (at high doses), recreational drug, pain killer, medicine for diarrhea, and treatment for opiate addiction drug since ancient times [81]. In Thailand, the natives have always used the plant for its effects similar to those of opioids and cocaine. Fresh leaves from the central rib are usually chewed; dried leaves can be chewed (generally after mincing or pulverizing) or smoked; both fresh and dried leaves can be boiled for a long time to prepare a paste-like compound that can be kept for a long time. At present, the dried and pulverized kratom leaves are used as legal stimulants or, instead of analgesics for its euphoric sedative effects [82-85]. Kratom preparations contain over 40 structurally related alkaloids, making their pharmacological and toxicological evaluation unique and difficult. The main psychoactive components in the leaves are the alkaloids mitragynine and 7-hydroxymitragynine both found only in *Mitragyna speciosa*, but other analogues have been identified (*e.g*., speciogynine, paynantheine, and speciociliatine) [86]. The effects of Kratom in humans are dose-dependent since small doses produce stimulatory effects resembling the stimulant effect of drugs such as cocaine or amphetamines, while larger dosages tend to be associated with sedative-narcotic effects that resemble drugs such as opiates [81, 85, 87]. As above reported, mitragynine is the principal alkaloid of *Mitragyna speciosa*. Chemically, mitragynine is the 9-methoxy-corynantheidine. The molecule is structurally related to both yohimbine (the stimulant alkaloid of *Pausinystalia yohimbe* plant) and to voacangine (the alkaloid of *Voacanga africana*). The molecular structure is somewhat similar to psilocibine type or LSD psychedelic drugs [88, 89].

It seems that the alkaloids content can change according to the geographical area, phases of the plant growth, and year seasons [89, 90]. It has been showed that mitragyne acts as agonist on the mu (μ), kappa (κ), and delta (δ) opioid receptors of the central nervous system, leading to depressing effects similar to opioids but with less intensity (about 26% compared to morphine); however since its structure does not resemble components of the opioid family, it has been suggested that mitragyne could present a more broad receptor binding activity [91]. Moreover, since mitragyne has only weak opiod effects, it has been suggest that also 7-hydroxymitragynine contributes to the plant properties. This alkaloid is highly potent and presents an affinity for the opioid receptors (particularly receptor μ) about 13 and 46 times higher than morphine and mitragynine, respectively [91].

Further studies have revealed how complex is Kratom's pharmacology, involving a κ-opioid and dopamine D1 receptors interaction in its various effects [92]. Serotonergic and adrenergic pathways have also been involved in the effects of mitragynine, mostly due to its broad affinity to different receptors [93]. Indeed, the pharmacological mechanisms responsible for stimulant activity are yet to be clearly established.

Kratom users report online that at low doses the preparation is rather stimulant, mind is "more alert," with increased physical energy and sometimes sexual arousal, and they also described "entactogenic" effects, like empathy and euphoria. Some people find this sensations anxiogenic rather than pleasant. At higher doses, experiences describe it as more sedative and analgesic: users prefer to be less sensitive to physical or emotional pain, to feel and look calm, and to have a general feeling of comfortable pleasure [83].

Users reported also a variety of less explored side-effects; including nausea, constipation, sleep problems, temporary erectile dysfunction, itching, and sweating and hyperpigmentation and tremor and anorexia and weight loss in long term consumption. Some others describe hair loss, probably related to a regular (daily) use of Kratom. Withdrawal symptoms are also common, including muscle aches, irritability, mood disturbances, runny nose, diarrhoea. Users describe tolerance (requiring the consumption of higher doses to achieve the same effects) and also a "cross-tolerance" to both kratom and opiates after repeated intake [83, 94].

Adverse effects and intoxications cases across various countries have also been reported, including liver toxicity, seizure, and coma, reports of patients suffering from intrahepatic cholestasis after two weeks of kratom use, adult respiratory distress syndrome, and hypothyroidism. Evidence also suggests that Kratom might be a deadly substance when mixed with other compounds [49, 94, 95-98].

Hallucinogenic Cacti from *Trichocereus* Family

The Trichocereus family includes about 40 cactecee plants. In South America there is an ancient cult tied to hallucinogenic cacti such as *Trichocereus pachanoi* (San Pedro), *peruvianus, werdermannianus, macrogonus,* and validus which grow in Perù and in Ecuador, particularly in the Andean regions [99]. The historical use is linked to the hallucinogenic content of mescaline, a phenethylamine structurally different from other major psychedelic drugs such as LSD, psilocibine, and DMT [100]. Mescaline is also the principal psychedelic alkaloid of another small, spineless cactus native to Mexico, *Lophophora williamsii* or peyote [100].

Mescaline acts in the central nervous system by stimulating the serotoninergic and dopaminergic receptor [101]; the mechanism that underlines cognitive, perceptive and affective effects is not still well know; however mescaline seems to be able to increased glutamate release at the level of the cerebral cortex by acting as a partial agonist of the 5-HT2A receptors for serotonine [2]. At the dose of 350 mg, the first effects of mescaline are observed at about 30 minutes after the ingestion, and can include nausea, vomiting, diarrhea, palpitations, tachycardia, increased blood pressure, mydriasis, obscured vision, breathing difficulties. Psychomimetic effects, like anxiety, visual and audio hallucinations, and alterations of spatial, temporal, sensory, tactile perceptions, [102] become noticeable about one hour after the intake; moreover the individual can show a strong empathy towards static objects or live organisms. The events and sensations are usually vividly remembered by the mescaline users [103].

Some cases described suicidal tendencies, fear, violent behaviours, paranoia, flashback episodes, and effects on the skin (*i.e*. flushing, diaphoresis, and piloerection) [104-108].

In a study on healthy volunteers it has been observed that the oral administration of a dose of 500 mg mescaline produced about 3-4 hours later an acute psychotic state for about 12-15 hours [105]. The smallest dose of mescaline which will likely produce a psychotic effect has been estimated at 200 mg given intramuscularly for an average user weight of 80 kg. A strong toxic effect is observed with approximately 3.75 mg/kg. The maximum toxic peak occurs within 2-4 hours post administration and it is resolved within the following 4-6 hours [109]. During the first two hours after administration, about 87% mescaline absorbed at intestinal level is excreted in urine; of this about 55-60% is excreted unchanged while 27-30% becomes metabolized to 3,4,5 trimethoxyphenylacetic acid and 5% is transformed into N-acetil-(3,4-dimethoxy-5-hydroxy)-phenylethylamine [107].

It has been observed that the association of mescaline and other drugs can lead to dependence and tolerance (defined as the reduction of the biological response to a constant dose of active component) [110]; for example a crossed tolerance can be induced by the assumption of mescaline with other hallucinogens such as LSD and psilocybin [111]. This tolerance can quickly decrease, within a couple of days of stopping the drug.

Convulsions, coma, rabdomyolisis and renal insufficiency have been described when mescaline was taken together with alcohol or methadone [112]. Anxiety, depression and persistent psychoses have been associated with the long term use of mescaline [113].

The use of mescaline is rarely lethal. In human, the toxic lethal dose with intramuscular administration is 2.5 mg/kg. There are two clinical cases in the literature describing fatalities related to the use of mescaline. In the first case the death has been caused by a trauma which occurred as a consequence of the drug induced delirium. The mescaline content in the blood and in the urine of patient were 9.7 μg/ml and 1163 μg/ml, respectively [114]. In the second case of a 32-year-old man, mescaline intoxication produced esophageal lacerations (Mallory-Weiss syndrome) with blood accumulation and marked pulmonary hemoaspiration causing the death). Mescaline plasma and urine concentration were 0.48 μg/ml and and 61 μg/ml, respectively. The Mallory-Weiss syndrome has been determined probably by the profuse vomiting induced by mescaline [115].

Salvia divinorum: The Magic Mint for Shamanistic Practices

Salvia divinorum (Hojas de Maria, Yerba Maria, Hierba de la pastora, Ska Maria pastora, Magic Mint, Diviner's sage) is a perennial plant belonging to the Lamiaceae family, native to Sierra Mazatec region of Mexico with a long history as a divinatory psychedelic compound [116]. It was traditionally taken by chewing, drinking or smoking by Mazated tribes as a potent hallucinogen. It has been remained relatively unknown as entheogen until the mid-1990s when Siebert [117, 118] firstly documented his self-experimental intake. It rapidly became easily available online where it is currently sold as dried leaves, extracts or live plants. It is usually ingested as an infusion, smoked or chewed its fresh leaves [119].

The hallucinogenic effect of *Salvia divinorum* is due to Salvinorin A, the principal psychoactive constituent of plant leaves [120]. Although Salvinorin A has a

pharmacological potency comparable to that of the synthetic hallucinogens such as LSD and DOB (4-bromo-2,5-dimethoxyphenylisopropylamine), the mechanism of action is different [121, 122]. In fact, *in vivo* and *in vitro* studies have showed that Salvinorin A has not any affinity for the serotonin 5-HT2A receptors, G-protein-coupled receptors, transporters, and ion channels canals that have been identified as principal molecular targets of the classic hallucinogens (LSD, N, N-dimethyltryptamine, psilocybin, mescaline); Salvinorin A is a powerful kappa (k) oppioid receptor agonist, whose stimulation seems to be related to the psychotropic effects associated with the consumption of *Salvia divinorum* extracts [121].

Salvia divinorum leaves can contain about 0.89 to 3.7 mg/g of dry weight of active substances, that are enough to induce psychoactive effects [123].

In traditional medicine, 4-5 fresh or dried leaves of *Salvia divinorum* have been used like tonic (to combat fatigue) and like a panacea, the only true medicine with magical properties. An hallucinogenic infusion can be obtained using 20-60 fresh leaves [124]. The hallucinations are usually visual, auditory and tactile and involve vision of two-dimensional surfaces, return to places of the past (particularly childhood), sensations of movement (to be pulled or twisted by an unknown force), sensations of loss of body or of identity, hysterical and uncontrollable laughter and distorted perception of reality (sensations of being in several places at the same time) [125].

These effects usually appear very quickly (approximately within 20-60 seconds after intake) and may last around 5-15 minutes, if smoked. While the leaves usually induces slower onset and longer duration, after oral intake [126]. Some clinical data reported long-term effects such déjà vu, hallucinogenic persistent perceptual disorder, toxic psychosis and other visual disturbances [127]. Neither a physical or psychological dependence has been reported for *Salvia divinorum*. Withdrawal effects following discontinuation have not been described. Adverse effects include headache, mild irritability, throat and lung irritation (when smoked), feelings of fear, panic, overly intense experiences, instability and increased perspiration [116]. A case of persistent psychosis characterized by echolalia (involuntary repetition of words or phrases spoken by others), paranoia, agitation and conflict of ideas was described in a young man of 21 years without past mental disorders who had smoked *Salvia divinorum* [128].

Tabernanthe iboga: The Psychedelic Sacred Wood

Tabernanthe iboga (Black bugbane, le bois sacre, sacred wood) is an Apocynaceous shrub Ibogaine, which grows in West Central Africa. Its principal psychoactive compound is ibogaine, a monoterpene indole hallucinogenic alkaloid extracted from the root bark of the plant [129].

Traditionally, it has been ritually used as a medicinal and ritual substance during the ceremony of initiation into adulthood, in the Bwiti religion [130, 131] Ibogaine was firstly isolated and crystallized from Tabernanthe Iboga root bark in 1901. In 1939, an Ibogaine-containing extract was sold in France as *Lambarène*, a neuromuscular stimulant for the treatment of fatigue, depression and recovery from infectious disease. Some Ibogaine-containing products have been subsequently marketed, including Bogadin, Iperton, Endabuse and Lambargene [131]. During the 1960s, the alkaloid was introduced as an anti-addiction agent in the detoxification treatment from opiates and craving to alleviate abstinence syndrome, craving and to speed up the tolerance reversion [132, 133].

Ibogaine is a long-lasting, strong psychedelic, dissociative and oneirogen alkaloid. At smaller doses, it is appreciated due to its stimulant and aphrodisiac properties [131, 134] Common route of administration is oral. The onset of symptoms is generally within 45 minutes-3 hours after ingestion and may last 24 hours or more. During the phase of intoxication, the subject may be immobilized [134].

Ibogaine interacts with multiple receptor sites within central nervous system, including the dopaminergic (noncompetitively agonist for the DAT), serotonergic (noncompetitively agonist for the 5-HT2A), nicotinic, GABA and muscarinic receptors as antagonist at N-methyl-D-aspartate receptors and agonist at the k-opioid receptors [134-137]. Ibogaine is metabolized by CYP450 into noribogaine (12-hydroxyibogamine), which is more potent by acting as a moderate k-opioid receptor antagonist and a weak antagonist/partial agonist at μ-opioid receptors [138].

Psychedelic effects usually consist of a 'triple-phase experience' constituted by a visionary (phase 1), an introspection (phase 2) and a residual phase (phase 3). The phase 1 appears within 1 to 3 hours of ingestion and lasts 4 to 8 hours. The predominant reported experiences appear to involve a panoramic readout of long-term memory and visions or states like a 'walking dream' featuring archetypical experiences (*e.g.*, transcendent beings, passage along a lengthy path or floating). Ibogaine-related visual experiences have been more frequently associated with eye closure, usually disappearing with eye opening. Phase 2 starts approximately 4 to 8 hours after ingestion, with a duration of 8 to 20 hours. The individuals reported a neutral and reflective emotional tone. The attention is usually focused on inner subjective experiences. During the residual stimulation (phase 3), approximately at 12 to 24 hours after ingestion, the intensity of subjective psychoactive experience lessens with mild residual subjective arousal/vigilance and the need to sleep [139].

Ibogaine untoward effects include ataxia, xerostomia, nausea, vomiting, QT-interval prolongation, arrhythmias, and cardiac arrest [140-144]. Neither a physical or psychological dependence, nor withdrawal effects following ibogaine discontinuation have not been described. Several fatalities and unexpected sudden cardiac death have been related to iIbogaine consumption [140, 142, 145, 146]. The results of the preclinical studies and anecdotal reports from addict self-help groups let hypothesized the use of ibogaine as drug in addiction therapy. Unfortunately, this just remain at a research level and drug was never introduced in standardized protocols of addiction treatments.The mechanism of action of ibogaine in the treatment of drug addiction has to be still clarified [134].

CONCLUSION

This review demonstrates that even if psychoactive plants have been known and used from ancient times, there is still limited information regarding subjective and neuropharmacological effects and consequent eventual toxicity when plants are used alone or in combination with "classical" drugs of abuse. For this reason, significant safety concerns should be raised on recreational use of these substances. The majority of the medical literature reporting abuse of herbals is anecdotal, and the short- and long-term effects of abuse are yet unrecognized.

If on the one hand the neuropharmacological effects of some of them are well established, on the other, one of the most important issue which still needs clarification is the risk of addiction due to the abuse of these compounds. For certain herbals chronic administration provides evidence for an addiction potential with cognitive impairments, which suggest its classification as a harmful drug; for some others taking into consideration only the recent trends of abuse, studies investigating these aspects are lacking.

CONFLICT OF INTEREST

The authors confirm that they do not have any conflicts of interest with this article contents.

ACKNOWLEDGEMENTS

The authors would like to thank Manuela Pellegrini and Emilia Marchei for their assistance during the preparation of the manuscript.

REFERENCES

[1] Rodríguez, S.B.; Gómez-Arnau R,J.; Sánchez, M,D.; Dolengevich S.H. [Vegetables as new psychoactive drugs: a narrative review]. *Medwave,* **2016**, *16*(1), e6372. [http://dx.doi.org/10.5867/medwave.2016.01.6372] [PMID: 26937890]

[2] *https://www.globaldrugsurvey.com/wp-content/uploads/2016/06/TASTER-KEY-FINDINGS-FROM-GDS2016.pdf,*

[3] Metzner, R. Hallucinogenic drugs and plants in psychotherapy and shamanism. *J. Psychoactive Drugs,* **1998**, *30*(4), 333-341. [http://dx.doi.org/10.1080/02791072.1998.10399709] [PMID: 9924839]

[4] Baumeister, D.; Tojo, L.M.; Tracy, D.K. Legal highs: staying on top of the flood of novel psychoactive substances. *Ther. Adv. Psychopharmacol.,* **2015**, *5*(2), 97-132. [http://dx.doi.org/10.1177/2045125314559539] [PMID: 26240749]

[5] Hess, C.; Schoeder, C.T.; Pillaiyar, T.; Madea, B.; Müller, C.E. Pharmacological evaluation of synthetic cannabinoids identified as constituents of spice. *Forensic Toxicol.,* **2016**, *34*, 329-343. [http://dx.doi.org/10.1007/s11419-016-0320-2] [PMID: 27429655]

[6] Domínguez-Clavé, E.; Soler, J.; Elices, M.; Pascual, J.C.; Álvarez, E.; de la Fuente Revenga, M.; Friedlander, P.; Feilding, A.; Riba, J. Ayahuasca: Pharmacology, neuroscience and therapeutic potential. *Brain Res. Bull.,* **2016**. pii: S0361-9230(16)30045-4. [Epub ahead of print]

[7] de Araujo, D.B.; Ribeiro, S.; Cecchi, G.A.; Carvalho, F.M.; Sanchez, T.A.; Pinto, J.P.; de Martinis, B.S.; Crippa, J.A.; Hallak, J.E.; Santos, A.C. Seeing with the eyes shut: neural basis of enhanced imagery following Ayahuasca ingestion. *Hum. Brain Mapp.,* **2012**, *33*(11), 2550-2560. [http://dx.doi.org/10.1002/hbm.21381] [PMID: 21922603]

[8] Samoylenko, V.; Rahman, M.M.; Tekwani, B.L.; Tripathi, L.M.; Wang, Y.H.; Khan, S.I.; Khan, I.A.; Miller, L.S.; Joshi, V.C.; Muhammad, I. Banisteriopsis caapi, a unique combination of MAO inhibitory and antioxidative constituents for the activities relevant to neurodegenerative disorders and Parkinsons disease. *J. Ethnopharmacol.,* **2010**, *127*(2), 357-367. [http://dx.doi.org/10.1016/j.jep.2009.10.030] [PMID: 19879939]

[9] Riba, J.; Rodríguez-Fornells, A.; Urbano, G.; Morte, A.; Antonijoan, R.; Montero, M.; Callaway, J.C.; Barbanoj, M.J. Subjective effects and tolerability of the South American psychoactive beverage Ayahuasca in healthy volunteers. *Psychopharmacology (Berl.),* **2001**, *154*(1), 85-95. [http://dx.doi.org/10.1007/s002130000606] [PMID: 11292011]

[10] Callaway, J.C.; Grob, C.S. Ayahuasca preparations and serotonin reuptake inhibitors: a potential combination for severe adverse interactions. *J. Psychoactive Drugs,* **1998**, *30*(4), 367-369. [http://dx.doi.org/10.1080/02791072.1998.10399712] [PMID: 9924842]

[11] Carbonaro, T.M.; Gatch, M.B. Neuropharmacology of N, N-dimethyltryptamine. *Brain Res Bull.,* **2016**. pii: S0361-9230(16)30090-9. [Epub ahead of print]

[12] González-Maeso, J.; Sealfon, S.C. Agonist-trafficking and hallucinogens. *Curr. Med. Chem.,* **2009**, *16*(8), 1017-1027. [http://dx.doi.org/10.2174/092986709787581851] [PMID: 19275609]

[13] González-Maeso, J.; Weisstaub, N.V.; Zhou, M.; Chan, P.; Ivic, L.; Ang, R.; Lira, A.; Bradley-Moore, M.; Ge, Y.; Zhou, Q.; Sealfon, S.C.; Gingrich, J.A. Hallucinogens recruit specific cortical 5-HT(2A) receptor-mediated signaling pathways to affect behavior. *Neuron,* **2007**, *53*(3), 439-452. [http://dx.doi.org/10.1016/j.neuron.2007.01.008] [PMID: 17270739]

[14] ODonovan, K.J.; Tourtellotte, W.G.; Millbrandt, J.; Baraban, J.M. The EGR family of transcription-regulatory factors: progress at the interface of molecular and systems neuroscience. *Trends Neurosci.,* **1999**, *22*(4), 167-173. [http://dx.doi.org/10.1016/S0166-2236(98)01343-5] [PMID: 10203854]

[15] Jones, M.W.; Errington, M.L.; French, P.J.; Fine, A.; Bliss, T.V.; Garel, S.; Charnay, P.; Bozon, B.; Laroche, S.; Davis, S. A requirement for the immediate early gene Zif268 in the expression of late LTP and long-term memories. *Nat. Neurosci.,* **2001**, *4*(3), 289-296. [http://dx.doi.org/10.1038/85138] [PMID: 11224546]

[16] DeSteno, D.A.; Schmauss, C. Induction of early growth response gene 2 expression in the forebrain of mice performing an attention-set-shifting task. *Neuroscience,* **2008**, *152*(2), 417-428. [http://dx.doi.org/10.1016/j.neuroscience.2008.01.012] [PMID: 18280047]

[17] Fontanilla, D.; Johannessen, M.; Hajipour, A.R.; Cozzi, N.V.; Jackson, M.B.; Ruoho, A.E. The hallucinogen N,N-dimethyltryptamine (DMT) is an endogenous sigma-1 receptor regulator. *Science,* **2009**, *323*(5916), 934-937. [http://dx.doi.org/10.1126/science.1166127] [PMID: 19213917]

[18] Bunzow, J.R.; Sonders, M.S.; Arttamangkul, S.; Harrison, L.M.; Zhang, G.; Quigley, D.I.; Darland, T.; Suchland, K.L.; Pasumamula, S.; Kennedy, J.L.; Olson, S.B.; Magenis, R.E.; Amara, S.G.; Grandy, D.K. Amphetamine, 3, 4-methylenedioxymethamphetamine, lysergic acid diethylamide, and metabolites of the catecholamine neurotransmitters are neurotransmitters areagonists of a rat trace amine receptor. *Mol. Pharmacol.,* **2001**, *60*, 1181-1188. [PMID: 11723224]

[19] Cozzi, N.V.; Gopalakrishnan, A.; Anderson, L.L.; Feih, J.T.; Shulgin, A.T.; Daley, P.F.; Ruoho, A.E. Dimethyltryptamine and other hallucinogenic tryptamines exhibit substrate behavior at the serotonin uptake transporter and the vesicle monoamine transporter. *J Neural. Transm. (Vienna),* **2009**, *116*(12), 1591-1599. [http://dx.doi.org/10.1007/s00702-009-0308-8] [PMID: 19756361]

[20] Bouso, J.C.; Palhano-Fontes, F.; Rodríguez-Fornells, A.; Ribeiro, S.; Sanches, R.; Crippa, J.A.; Hallak, J.E.; de Araujo, D.B.; Riba, J. Long-term use of psychedelic drugs is associated with differences in brain structure and personality in humans. *Eur. Neuropsychopharmacol.,* **2015**, *25*(4), 483-492. [http://dx.doi.org/10.1016/j.euroneuro.2015.01.008] [PMID: 25637267]

[21] Sanches, R.F.; de Lima Osório, F.; Dos Santos, R.G.; Macedo, L.R.; Maia-de-Oliveira, J.P.; Wichert-Ana, L.; de Araujo, D.B.; Riba, J.; Crippa, J.A.; Hallak, J.E. Antidepressant effects of a single Dose of ayahuasca in patients with recurrentdepression: a SPECT study. *J. Clin. Psychopharmacol.,* **2016**, *36*(1), 77-81. [http://dx.doi.org/10.1097/JCP.0000000000000436] [PMID: 26650973]

[22] Buckholtz, N.S.; Boggan, W.O. Inhibition by beta-carbolines of monoamine uptake into a synaptosomal preparation: structure-activity relationships. *Life Sci.,* **1977**, *20*(12), 2093-2099. [http://dx.doi.org/10.1016/0024-3205(77)90190-4] [PMID: 18641]

[23] *Anonyms. The Ayurvedic Pharmacopoeia of India, Government of India*; Department of ISM and H, M/O Health and Family Welfare: New Delhi, **2006**, pp. 16-18.

[24] Modi, A.J.; Khadabadi, S.S.; Deokata, U.A.; Farooqui, I.A.; Deore, S.L.; Gangwani, M.R. Argyreia speciosa Linn. F.: Phytochemistry, pharmacognosy and pharmacological studies. *J. Pharmacogn. Phytother.,* **2010**, *2*, 34-42.

[25] Srivastava, A.; Shukla, Y.N.; Jain, S.P.; Kumar, S. Chemistry and pharmacology of Argyreia speciosa - A review. *J. Med. Aromat. Plant Sci.,* **1998**, *20*, 774-778.

[26] Duke, J.A. *Handbook of medicinal herbs*; CRC Press, **2002**. [http://dx.doi.org/10.1201/9781420040463]

[27] Paulke, A.; Kremer, C.; Wunder, C.; Wurglics, M.; Schubert-Zsilavecz, M.; Toennes, S.W. Studies on the alkaloid composition of the Hawaiian Baby Woodrose *Argyreia nervosa*, a common legal high. *Forensic Sci. Int.,* **2015**, *249*, 281-293. [http://dx.doi.org/10.1016/j.forsciint.2015.02.011] [PMID: 25747328]

[28] Der Marderosian, A.; Yougken, H.W. The distribution of indole alkaloids among certain species and varieties of Ipomoea, Rivea and Convolvolus (Convolvulaceae). *Llodia,* **1966**, *29*, 35-42.

[29] Chao, J.M.; Der Marderosian, A.H. Ergoline alkaloidal constituents of Hawaiian baby wood rose, *Argyreia nervosa* (Burm. f.) Bojer. *J. Pharm. Sci.,* **1973**, *62*(4), 588-591. [http://dx.doi.org/10.1002/jps.2600620409] [PMID: 4698977]

[30] Srivastava, A.; Shukla, Y.N.; Jain, S.P.; Kumar, S. Chemistry and pharmacology of the elephant creeper *Argyreia speciosa* - a review. *J. Med. Arom. Plant. Sci.,* **1998**, *20*, 774-778.

[31] Halpern, J.H. Hallucinogens and dissociative agents naturally growing in the United States. *Pharmacol. Ther.,* **2004**, *102*(2), 131-138. [http://dx.doi.org/10.1016/j.pharmthera.2004.03.003] [PMID: 15163594]

[32] Hylin, J.W.; Watson, D.P. Ergoline alkaloids in tropical wood roses. *Science,* **1965**, *148*(3669), 499-500. [http://dx.doi.org/10.1126/science.148.3669.499] [PMID: 17842841]

[33] Genest, K. Changes in ergoline alkaloids in seeds during ontogeny of Ipomoea violacea. *J. Pharm. Sci.,* **1966**, *55*(11), 1284-1288. [http://dx.doi.org/10.1002/jps.2600551123] [PMID: 5969787]

[34] Larson, B.T.; Harmon, D.L.; Piper, E.L.; Griffis, L.M.; Bush, L.P. Alkaloid binding and activation of D2 dopamine receptors in cell culture. *J. Anim. Sci.,* **1999**, *77*(4), 942-947. [http://dx.doi.org/10.2527/1999.774942x] [PMID: 10328360]

[35] Göpel, C.; Maras, A.; Schmidt, M.H. [Hawaiian baby rose wood: case report of an argyreia nervosa induced toxic psychosis]. *Psychiatr. Prax.,* **2003**, *30*(4), 223-224. [Hawaiian baby rose wood: case report of an argyreia nervosa induced toxic psychosis]. [PMID: 12768530]

[36] Gertsch, J.H.; Wood, C. Case report: an ingestion of Hawaiian Baby Woodrose seeds associated with acute psychosis. *Hawaii Med. J.,* **2003**, *62*(6), 127-129, 129. [PMID: 12886727]

[37] Kremer, C.; Paulke, A.; Wunder, C.; Toennes, S.W. Variable adverse effects in subjects after ingestion of equal doses of Argyreia nervosa seeds. *Forensic Sci. Int.,* **2012**, *214*(1-3), e6-e8. [http://dx.doi.org/10.1016/j.forsciint.2011.06.025] [PMID: 21803515]

[38] Patel, N.B. Natural Amphetamine Khat: A Cultural Tradition or a Drug of Abuse? *Int. Rev. Neurobiol.,* **2015**, *120*, 235-255. [http://dx.doi.org/10.1016/bs.irn.2015.02.006] [PMID: 26070760]

[39] Patel, N.B. Mechanism of action of cathinone: the active ingredient of khat (*Catha edulis*). *East Afr. Med. J.,* **2000**, *77*(6), 329-332. [PMID: 12858935]

[40] Kalix, P. Recent advances in khat research. *Alcohol Alcohol.,* **1984**, *19*(4), 319-323. [PMID: 6398076]

[41] Nencini, P.; Ahmed, A.M. Khat consumption: a pharmacological review. *Drug Alcohol Depend.,* **1989**, *23*(1), 19-29. [http://dx.doi.org/10.1016/0376-8716(89)90029-X] [PMID: 2537717]

[42] Al-Hebshi, N.N.; Skaug, N. Khat (*Catha edulis*)-an updated review. *Addict. Biol.,* **2005**, *10*(4), 299-307. [http://dx.doi.org/10.1080/13556210500353020] [PMID: 16318950]

[43] Toennes, S.W.; Kauert, G.F. Driving under the influence of khatalkaloid concentrations and observations in forensic cases. *Forensic Sci. Int.,* **2004**, *140*(1), 85-90. [http://dx.doi.org/10.1016/j.forsciint.2003.11.028] [PMID: 15013169]

[44] Bentur, Y.; Bloom-Krasik, A.; Raikhlin-Eisenkraft, B. Illicit cathinone ("Hagigat") poisoning. *Clin. Toxicol.,* **2007**, *15*, 1-5.

[45] *http://www.emcdda.europa.eu/publications/drug-profiles/khat,* (Accessed 11 August 2016)

[46] Toennes, S.W.; Harder, S.; Schramm, M.; Niess, C.; Kauert, G.F. Pharmacokinetics of cathinone, cathine and norephedrine after the chewing of khat leaves. *Br. J. Clin. Pharmacol.,* **2003**, *56*(1), 125-130. [http://dx.doi.org/10.1046/j.1365-2125.2003.01834.x] [PMID: 12848785]

[47] Girma, T.; Mossie, A.; Getu, Y. Association between body composition and khat chewing in Ethiopian adults. *BMC Res. Notes,* **2015**, *8*, 680. [http://dx.doi.org/10.1186/s13104-015-1601-2] [PMID: 26578211]

[48] El-Menyar, A.; Mekkodathil, A.; Al-Thani, H.; Al-Motarreb, A. Khat use: history and heart failure. *Oman Med. J.,* **2015**, *30*(2), 77-82. [http://dx.doi.org/10.5001/omj.2015.18] [PMID: 25960830]

[49] Pantano, F.; Tittarelli, R.; Mannocchi, G.; Zaami, S.; Ricci, S.; Giorgetti, R.; Terranova, D.; Busardò, F.P.; Marinelli, E. Hepatotoxicity Induced by the 3Ks: Kava, Kratom and Khat. *Int. J. Mol. Sci.,* **2016**, *17*(4), 580. [http://dx.doi.org/10.3390/ijms17040580] [PMID: 27092496]

[50] Feyissa, A.M.; Kelly, J.P. A review of the neuropharmacological properties of khat. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2008**, *32*(5), 1147-1166. [http://dx.doi.org/10.1016/j.pnpbp.2007.12.033] [PMID: 18561890]

[51] Ellison, G. Neural degeneration following chronic stimulant abuse reveals a weak link in brain, fasciculus retroflexus, implying the loss of forebrain control circuitry. *Eur. Neuropsychopharmacol.,* **2002**, *12*(4), 287-297. [http://dx.doi.org/10.1016/S0924-977X(02)00020-2] [PMID: 12126867]

[52] Giannini, A.J.; Castellani, S. A manic-like psychosis due to khat (Catha edulis Forsk.). *J. Toxicol. Clin. Toxicol.,* **1982**, *19*(5), 455-459. [http://dx.doi.org/10.3109/15563658208992500] [PMID: 7175990]

[53] Odenwald, M.; Neuner, F.; Schauer, M.; Elbert, T.; Catani, C.; Lingenfelder, B.; Hinkel, H.; Häfner, H.; Rockstroh, B. Khat use as risk factor for psychotic disorders: a cross-sectional and case-control study in Somalia. *BMC Med.,* **2005**, *3*, 5. [http://dx.doi.org/10.1186/1741-7015-3-5] [PMID: 15707502]

[54] Soni, P.; Siddiqui, A.A.; Dwivedi, J.; Soni, V. Pharmacological properties of *Datura stramonium* L. as a potential medicinal tree: an overview. *Asian Pac. J. Trop. Biomed.,* **2012**, *2*(12), 1002-1008. [http://dx.doi.org/10.1016/S2221-1691(13)60014-3] [PMID: 23593583]

[55] Francis, P.D.; Clarke, C.F. Angel trumpet lily poisoning in five adolescents: clinical findings and management. *J. Paediatr. Child Health,* **1999**, *35*(1), 93-95. [http://dx.doi.org/10.1046/j.1440-1754.1999.00328.x] [PMID: 10234644]

[56] Taiwo, M.A.; Hughes, J.A.; Akomah, A.R. Natural Infection of *Datura stramonium* L. By an Unusual Strain of Pepper veinal mottle virus Genus Potyvirus in Nigeria. *Plant Pathol. J.,* **2006**, *5*, 401-404. [http://dx.doi.org/10.3923/ppj.2006.401.404]

[57] Dessanges, J.F. A history of nebulization. *J. Aerosol Med.,* **2001**, *14*(1), 65-71. [http://dx.doi.org/10.1089/08942680152007918] [PMID: 11495487]

[58] Şanlıdağ, B.; Derinöz, O.; Yıldız, N. A case of pediatric age anticholinergic intoxication due to accidental *Datura stramonium* ingestion admitting with visual hallucination. *Turk. J. Pediatr.,* **2014**, *56*(3), 313-315. [PMID: 25341608]

[59] Stella, L.; Vitelli, M.R.; Palazzo, E.; Oliva, P.; De Novellis, V.; Capuano, A.; Scafuro, M.A.; Berrino, L.; Rossi, F.; Maione, S. *Datura stramonium* intake: a report on three cases. *J. Psychoactive Drugs,* **2010**, *42*(4), 507-512. [http://dx.doi.org/10.1080/02791072.2010.10400713] [PMID: 21305915]

[60] Gaire, B.P.; Subedi, L. A review on the pharmacological and toxicological aspects of *Datura stramonium* L. *J. Integr. Med.,* **2013**, *11*(2), 73-79. [http://dx.doi.org/10.3736/jintegrmed2013016] [PMID: 23506688]

[61] Vearrier, D.; Greenberg, M.I. Anticholinergic delirium following *Datura stramonium* ingestion: Implications for the Internet age. *J. Emerg. Trauma Shock,* **2010**, *3*(3), 303. [http://dx.doi.org/10.4103/0974-2700.66565] [PMID: 20930988]

[62] Adegoke, S.A.; Alo, L.A. *Datura stramonium* poisoning in children. *Niger. J. Clin. Pract.,* **2013**, *16*(1), 116-118. [http://dx.doi.org/10.4103/1119-3077.106783] [PMID: 23377485]

[63] Khanra, S.; Khess, C.R.; Srivastava, N. Chronic non-fatal Datura abuse in a patient of paranoid schizophrenia: a case report. *Addict. Behav.,* **2015**, *43*, 39-41. [http://dx.doi.org/10.1016/j.addbeh.2014.12.002] [PMID: 25544354]

[64] Boumba, V.A.; Mitselou, A.; Vougiouklakis, T. Fatal poisoning from ingestion of *Datura stramonium* seeds. *Vet. Hum. Toxicol.,* **2004**, *46*(2), 81-82. [PMID: 15080209]

[65] DeFrates, L.J.; Hoehns, J.D.; Sakornbut, E.L.; Glascock, D.G.; Tew, A.R. Antimuscarinic intoxication resulting from the ingestion of moonflower seeds. *Ann. Pharmacother.,* **2005**, *39*(1), 173-176. [http://dx.doi.org/10.1345/aph.1D536] [PMID: 15572604]

[66] Parissis, D.; Mellidis, C.; Boutis, A.; Apostolidis, K.; Ignatiadis, M.; Kiosses, V.; Milonas, I. Neurological findings in a case of coma secondary to *Datura stramonium* poisoning. *Eur. J. Neurol.,* **2003**, *10*(6), 745-746. [http://dx.doi.org/10.1046/j.1468-1331.2003.00614.x] [PMID: 14641526]

[67] Singh, Y.N. Kava: an overview. *J. Ethnopharmacol.,* **1992**, *37*(1), 13-45. [http://dx.doi.org/10.1016/0378-8741(92)90003-A] [PMID: 1453702]

[68] Leach, M.J.; Page, A.T. Herbal medicine for insomnia: A systematic review and meta-analysis. *Sleep Med. Rev.,* **2015**, *24*, 1-12. [http://dx.doi.org/10.1016/j.smrv.2014.12.003] [PMID: 25644982]

[69] Shi, Y.; Dong, J.W.; Zhao, J.H.; Tang, L.N.; Zhang, J.J. Herbal Insomnia Medications that Target GABAergic Systems: A Review of the Psychopharmacological Evidence. *Curr. Neuropharmacol.,* **2014**, *12*(3), 289-302. [http://dx.doi.org/10.2174/1570159X11666131227001243] [PMID: 24851093]

[70] Savage, K.M.; Stough, C.K.; Byrne, G.J.; Scholey, A.; Bousman, C.; Murphy, J.; Macdonald, P.; Suo, C.; Hughes, M.; Thomas, S.; Teschke, R.; Xing, C.; Sarris, J. Kava for the treatment of generalised anxiety disorder (K-GAD): study protocol for a randomised controlled trial. *Trials,* **2015**, *16*, 493. [http://dx.doi.org/10.1186/s13063-015-0986-5] [PMID: 26527536]

[71] Cairney, S.; Maruff, P.; Clough, A.R. The neurobehavioural effects of kava. *Aust. N. Z. J. Psychiatry,* **2002**, *36*(5), 657-662. [http://dx.doi.org/10.1046/j.1440-1614.2002.01027.x] [PMID: 12225450]

[72] Ramzan, I.; Tran, V. Chemistry of kava And kavalactones. In: *Kava from Ethnology to Pharmacology*; Singh, Y.N., Ed.; CRC Press, **2004**; pp. 76-103.

[73] Chua, H.C.; Christensen, E.T.; Hoestgaard-Jensen, K.; Hartiadi, L.Y.; Ramzan, I.; Jensen, A.A.; Absalom, N.L.; Chebib, M. Kavain, the Major Constituent of the Anxiolytic Kava Extract, Potentiates GABAA Receptors: Functional Characteristics and Molecular Mechanism. *PLoS One,* **2016**, *11*(6), e0157700. [http://dx.doi.org/10.1371/journal.pone.0157700] [PMID: 27332705]

[74] Tang, X.; Amar, S. Kavain Involvement in LPS-Induced Signaling Pathways. *J. Cell. Biochem.,* **2016**, *117*(10), 2272-2280. Epub ahead of print [http://dx.doi.org/10.1002/jcb.25525] [PMID: 26917453]

[75] Tang, X.; Amar, S. Kavain Inhibition of LPS-Induced TNF-α *via* ERK/LITAF. *Toxicol. Res. (Camb.),* **2016**, *5*(1), 188-196. [http://dx.doi.org/10.1039/C5TX00164A] [PMID: 26918116]

[76] Ernst, E. The risk-benefit profile of commonly used herbal therapies: Ginkgo, St. Johns Wort, Ginseng, Echinacea, Saw Palmetto, and Kava. *Ann. Intern. Med.,* **2002**, *136*(1), 42-53. [http://dx.doi.org/10.7326/0003-4819-136-1-200201010-00010] [PMID: 11777363]

[77] Spillane, P.K.; Fisher, D.A.; Currie, B.J. Neurological manifestations of kava intoxication. *Med. J. Aust.,* **1997**, *167*(3), 172-173. [PMID: 9269278]

[78] Anke, J.; Ramzan, I. Pharmacokinetic and pharmacodynamic drug interactions with Kava (*Piper methysticum* Forst. f.). *J. Ethnopharmacol.,* **2004**, *93*(2-3), 153-160. [http://dx.doi.org/10.1016/j.jep.2004.04.009] [PMID: 15234747]

[79] Li, X.Z.; Ramzan, I. Role of ethanol in kava hepatotoxicity. *Phytother. Res.,* **2010**, *24*(4), 475-480. [PMID: 19943335]

[80] Ketola, R.A.; Viinamäki, J.; Rasanen, I.; Pelander, A.; Goebeler, S. Fatal kavalactone intoxication by suicidal intravenous injection. *Forensic Sci. Int.,* **2015**, *249*, e7-e11. [http://dx.doi.org/10.1016/j.forsciint.2015.01.032] [PMID: 25684328]

[81] Prozialeck, W.C.; Jivan, J.K.; Andurkar, S.V. Pharmacology of kratom: an emerging botanical agent with stimulant, analgesic and opioid-like effects. *J. Am. Osteopath. Assoc.,* **2012**, *112*(12), 792-799. [PMID: 23212430]

[82] Singh, D.; Müller, C.P.; Vicknasingam, B.K.; Mansor, S.M. Social Functioning of Kratom (*Mitragyna speciosa*) Users in Malaysia. *J. Psychoactive Drugs,* **2015**, *47*(2), 125-131. [http://dx.doi.org/10.1080/02791072.2015.1012610] [PMID: 25950592]

[83] Cinosi, E.; Martinotti, G.; Simonato, P.; Singh, D.; Demetrovics, Z.; Roman-Urrestarazu, A.; Bersani, F.S.; Vicknasingam, B.; Piazzon, G.; Li, J.H.; Yu, W.J.; Kapitány-Fövény, M.; Farkas, J.; Di Giannantonio, M.; Corazza, O. Following the Roots of Kratom (*Mitragyna speciosa*): The Evolution of an Enhancer from a Traditional Use to Increase Work and Productivity in Southeast Asia to a Recreational Psychoactive Drug in Western Countries. *BioMed Res. Int.,* **2015**, *2015*, 968786. [http://dx.doi.org/10.1155/2015/968786] [PMID: 26640804]

[84] Adkins, J.E.; Boyer, E.W.; McCurdy, C.R. *Mitragyna speciosa*, a psychoactive tree from Southeast Asia with opioid activity. *Curr. Top. Med. Chem.,* **2011**, *11*(9), 1165-1175. [http://dx.doi.org/10.2174/156802611795371305] [PMID: 21050173]

[85] Warner, M.L.; Kaufman, N.C.; Grundmann, O. The pharmacology and toxicology of kratom: from traditional herb to drug of abuse. *Int. J. Legal Med.,* **2016**, *130*(1), 127-138. [http://dx.doi.org/10.1007/s00414-015-1279-y] [PMID: 26511390]

[86] EMCDDA (European Monitoring Centre for Drugs and Drug Addiction)—Kratom Drug profile. *http://www.emcdda.europa.eu/publications/drug-profiles/kratom,* (Accessed August 12, 2016)

[87] Suhaimi, F.W.; Yusoff, N.H.; Hassan, R.; Mansor, S.M.; Navaratnam, V.; Müller, C.P.; Hassan, Z. Neurobiology of Kratom and its main alkaloid mitragynine. *Brain Res Bull.,* **2016**. pii: S0361-9230(16)30058-2. [ahead of print] [http://dx.doi.org/10.1016/j.brainresbull.2016.03.015]

[88] Shellard, E.J. The alkaloids of Mitragyna with special reference to those of Mitragyna speciosa, Korth. *Bull. Narc.,* **1974**, *26*(2), 41-55. [PMID: 4607551]

[89] Takayama, H. Chemistry and pharmacology of analgesic indole alkaloids from the rubiaceous plant, *Mitragyna speciosa*. *Chem. Pharm. Bull. (Tokyo),* **2004**, *52*(8), 916-928. [http://dx.doi.org/10.1248/cpb.52.916] [PMID: 15304982]

[90] Ponglux, D.; Wongseripipatana, S.; Takayama, H.; Kikuchi, M.; Kurihara, M.; Kitajima, M.; Aimi, N.; Sakai, S. A new indole alkaloid, 7α-hydroxy-7H-mitragynine, from *Mitragyna speciosa* in Thailand. *Planta Med.,* **1994**, *60*(6), 580-581. [http://dx.doi.org/10.1055/s-2006-959578] [PMID: 17236085]

[91] Takayama, H.; Ishikawa, H.; Kurihara, M.; Kitajima, M.; Aimi, N.; Ponglux, D.; Koyama, F.; Matsumoto, K.; Moriyama, T.; Yamamoto, L.T.; Watanabe, K.; Murayama, T.; Horie, S. Studies on the synthesis and opioid agonistic activities of mitragynine-related indole alkaloids: discovery of opioid agonists structurally different from other opioid ligands. *J. Med. Chem.,* **2002**, *45*(9), 1949-1956. [http://dx.doi.org/10.1021/jm010576e] [PMID: 11960505]

[92] Stolt, A.C.; Schröder, H.; Neurath, H.; Grecksch, G.; Höllt, V.; Meyer, M.R.; Maurer, H.H.; Ziebolz, N.; Havemann-Reinecke, U.; Becker, A. Behavioral and neurochemical characterization of kratom (*Mitragyna speciosa*) extract. *Psychopharmacology (Berl.),* **2014**, *231*(1), 13-25. [Berl]. [http://dx.doi.org/10.1007/s00213-013-3201-y] [PMID: 23846544]

[93] Matsumoto, K.; Mizowaki, M.; Suchitra, T.; Murakami, Y.; Takayama, H.; Sakai, S.; Aimi, N.; Watanabe, H. Central antinociceptive effects of mitragynine in mice: contribution of descending noradrenergic and serotonergic systems. *Eur. J. Pharmacol.,* **1996**, *317*(1), 75-81. [http://dx.doi.org/10.1016/S0014-2999(96)00714-5] [PMID: 8982722]

[94] Swogger, M.T.; Hart, E.; Erowid, F.; Erowid, E.; Trabold, N.; Yee, K.; Parkhurst, K.A.; Priddy, B.M.; Walsh, Z. Experiences of Kratom Users: A Qualitative Analysis. *J. Psychoactive Drugs,* **2015**, *47*(5), 360-367. [http://dx.doi.org/10.1080/02791072.2015.1096434] [PMID: 26595229]

[95] Yusoff, N.H.; Suhaimi, F.W.; Vadivelu, R.K.; Hassan, Z.; Rümler, A.; Rotter, A.; Amato, D.; Dringenberg, H.C.; Mansor, S.M.; Navaratnam, V.; Müller, C.P. Abuse potential and adverse cognitive effects of mitragynine (kratom). *Addict. Biol.,* **2016**, *21*(1), 98-110. [http://dx.doi.org/10.1111/adb.12185] [PMID: 25262913]

[96] Galbis-Reig, D. A Case Report of Kratom Addiction and Withdrawal. *WMJ,* **2016**, *115*(1), 49-52. [PMID: 27057581]

[97] Dorman, C.; Wong, M.; Khan, A. Cholestatic hepatitis from prolonged kratom use: a case report. *Hepatology,* **2015**, *61*(3), 1086-1087. [http://dx.doi.org/10.1002/hep.27612] [PMID: 25418457]

[98] Singh, D.; Müller, C.P.; Vicknasingam, B.K. Kratom (*Mitragyna speciosa*) dependence, withdrawal symptoms and craving in regular users. *Drug Alcohol Depend.,* **2014**, *139*, 132-137. [http://dx.doi.org/10.1016/j.drugalcdep.2014.03.017] [PMID: 24698080]

[99] Carod-Artal, F.J. Hallucinogenic drugs in pre-Columbian Mesoamerican cultures. *Neurologia,* **2015**, *30*(1), 42-49. [http://dx.doi.org/10.1016/j.nrl.2011.07.003] [PMID: 21893367]

[100] Kovar, K.A. Chemistry and pharmacology of hallucinogens, entactogens and stimulants. *Pharmacopsychiatry,* **1998**, *31*(Suppl. 2), 69-72. [http://dx.doi.org/10.1055/s-2007-979349] [PMID: 9754836]

[101] Trulson, M.E.; Crisp, T.; Henderson, L.J. Mescaline elicits behavioral effects in cats by an action at both serotonin and dopamine receptors. *Eur. J. Pharmacol.,* **1983**, *96*(1-2), 151-154. [http://dx.doi.org/10.1016/0014-2999(83)90544-7] [PMID: 6581976]

[102] Aghajanian, G.K.; Marek, G.J. Serotonin and hallucinogens. *Neuropsychopharmacology,* **1999**, *21*(2)(Suppl.), 16S-23S. [http://dx.doi.org/10.1016/S0893-133X(98)00135-3] [PMID: 10432484]

[103] Shulgin, A.T. Mescaline: the chemistry and pharmacology of its analogs. *Lloydia,* **1973**, *36*(1), 46-58. [PMID: 4576313]

[104] Kapadia, G.J.; Fayez, M.B. Peyote constituents: chemistry, biogenesis, and biological effects. *J. Pharm. Sci.,* **1970**, *59*(12), 1699-1727. [http://dx.doi.org/10.1002/jps.2600591202] [PMID: 5499699]

[105] Ludwig, A.M.; Levine, J. Patterns of hallucinogenic drug abuse. *JAMA,* **1965**, *191*, 92-96. [http://dx.doi.org/10.1001/jama.1965.03080020020006] [PMID: 14233246]

[106] Jacobsen, E. The clinical pharmacology of the hallucinogens. *Clin. Pharmacol. Ther.,* **1963**, *4*, 480-503. [http://dx.doi.org/10.1002/cpt196344480] [PMID: 13964335]

[107] Hollister, L.E.; Hartman, A.M. Mescaline, lysergic acid diethylamide and psilocybin comparison of clinical syndromes, effects on color perception and biochemical measures. *Compr. Psychiatry,* **1962**, *3*, 235-242. [http://dx.doi.org/10.1016/S0010-440X(62)80024-8] [PMID: 13908449]

[108] Teitelbaum, D.T.; Wingeleth, D.C. Diagnosis and management of recreational mescaline self-poisoning. *J. Anal. Toxicol.,* **1977**, *1*, 36-37. [http://dx.doi.org/10.1093/jat/1.1.36]

[109] Jacobsen, E. The clinical pharmacology of the hallucinogens. *Clin. Pharmacol. Ther.,* **1963**, *4*, 480-503. [http://dx.doi.org/10.1002/cpt196344480] [PMID: 13964335]

[110] Schwartz, R.H. Mescaline: a survey. *Am. Fam. Phys.,* **1988**, *37*(4), 122-124. [PMID: 3358338]

[111] Martin, W.R.; Sloan, J.W. Pharmacology and classification of LSD-like hallucinogens. In: *Drug Addiction II: Amphetamine, Psychotogen, and Marihuana Dependence, Handbuch der Experimentellen Pharmacologie, 42 Pt 2*; Martin, W.R., Ed.; Springer-Verlag, **1977**; p. 368. [http://dx.doi.org/10.1007/978-3-642-66709-1_3]

[112] Jellin, J.M.; Gregory, P.; Batz, F. *Pharmacist's Letter/Prescribers's Letter Natural Medicines Comprehensive Database,* 3rd ed; Therapeutic Research Faculty: Stockton, CA, **2000**, p. 825.

[113] Kleber, H.D. Prolonged adverse reactions from unsupervised use of hallucinogenic drugs. *J. Nerv. Ment. Dis.,* **1967**, *144*, 308-319. [http://dx.doi.org/10.1097/00005053-196704000-00010]

[114] Reynolds, P.C.; Jindrich, E.J. A mescaline associated fatality. *J. Anal. Toxicol.,* **1985**, *9*(4), 183-184. [http://dx.doi.org/10.1093/jat/9.4.183] [PMID: 4033076]

[115] Nolte, K.B.; Zumwalt, R.E. Fatal peyote ingestion associated with Mallory-Weiss lacerations. *West. J. Med.,* **1999**, *170*(6), 328. [PMID: 10443159]

[116] Mahendran, R.; Lim, H.A.; Tan, J.Y.; Chua, S.M.; Winslow, M. Salvia divinorum: An overview of the usage, misuse, and addiction processes. *Asia-Pac. Psychiatry,* **2016**, *8*(1), 23-31. [http://dx.doi.org/10.1111/appy.12225] [PMID: 26617400]

[117] Siebert, D.J. *Salvia divinorum* and salvinorin A: new pharmacologic findings. *J. Ethnopharmacol.,* **1994**, *43*(1), 53-56. [http://dx.doi.org/10.1016/0378-8741(94)90116-3] [PMID: 7526076]

[118] Siebert, D.J. The history of the first *Salvia divinorum* plants cultivated outside of Mexico. *Entheogen Rev.,* **2004**, *12*, 117-118.

[119] Zawilska, J.B.; Wojcieszak, J. *Salvia divinorum*: from Mazatec medicinal and hallucinogenic plant to emerging recreational drug. *Hum. Psychopharmacol.,* **2013**, *28*(5), 403-412. [http://dx.doi.org/10.1002/hup.2304] [PMID: 23794315]

[120] MacLean, K.A.; Johnson, M.W.; Reissig, C.J.; Prisinzano, T.E.; Griffiths, R.R. Dose-related effects of salvinorin A in humans: dissociative, hallucinogenic, and memory effects. *Psychopharmacology (Berl.),* **2013**, *226*(2), 381-392. [http://dx.doi.org/10.1007/s00213-012-2912-9] [PMID: 23135605]

[121] Roth, B.L.; Baner, K.; Westkaemper, R.; Siebert, D.; Rice, K.C.; Steinberg, S.; Ernsberger, P.; Rothman, R.B. Salvinorin A: a potent naturally occurring nonnitrogenous kappa opioid selective agonist. *Proc. Natl. Acad. Sci. USA,* **2002**, *99*(18), 11934-11939. [http://dx.doi.org/10.1073/pnas.182234399] [PMID: 12192085]

[122] Pichini, S.; Abanades, S.; Farré, M.; Pellegrini, M.; Marchei, E.; Pacifici, R.; Torre, Rde.L.; Zuccaro, P. Quantification of the plant-derived hallucinogen Salvinorin A in conventional and non-conventional biological fluids by gas chromatography/mass spectrometry after *Salvia divinorum* smoking. *Rapid Commun. Mass Spectrom.,* **2005**, *19*(12), 1649-1656. [http://dx.doi.org/10.1002/rcm.1970] [PMID: 15915477]

[123] Gruber, J.W.; Siebert, D.J.; Der Marderosian, A.H.; Hock, R.S. High performance liquid chromatographic quantification of Salvinorin A from tissues of *Salvia divinorum* Epling & Jativa-M. *Phytochem. Anal.,* **1999**, *10*, 22-25. [http://dx.doi.org/10.1002/(SICI)1099-1565(199901/02)10:1<22::AID-PCA428>3.0.CO;2-0]

[124] Valdes, L.J.; Hatfield, G.M.; Koreeda, M.; Paul, A.G. Studies of *Salvia divinorum* (Lamiaceae), an hallucinogenic mint from the *Sierra Mazateca* in Oaxaca, Central Mexico. *Econ. Bot.,* **1987**, *41*, 283-291. [http://dx.doi.org/10.1007/BF02858975]

[125] Valdés, L.J., III; Díaz, J.L.; Paul, A.G. Ethnopharmacology of ska María Pastora (*Salvia divinorum*, Epling and Játiva-M.). *J. Ethnopharmacol.,* **1983**, *7*(3), 287-312. [http://dx.doi.org/10.1016/0378-8741(83)90004-1] [PMID: 6876852]

[126] McClatchey, W.C.; Mahady, G.B.; Bennett, B.C.; Shiels, L.; Savo, V. Ethnobotany as a pharmacological research tool and recent developments in CNS-active natural products from ethnobotanical sources. *Pharmacol. Ther.,* **2009**, *123*(2), 239-254. [http://dx.doi.org/10.1016/j.pharmthera.2009.04.002] [PMID: 19422851]

[127] Scheider, R.J.; Ardenghi, P. *Salvia divinorum* Epling and Jàtiva ('ska Maria Pastora') and Salvinorina A: increasing recreational use and abuse potential. *Rev Bras Plantas Med.,* **2010**, *12*, 358-362. [http://dx.doi.org/10.1590/S1516-05722010000300014]

[128] Przekop, P.; Lee, T. Persistent psychosis associated with *salvia divinorum* use. *Am. J. Psychiatry,* **2009**, *166*(7), 832. [http://dx.doi.org/10.1176/appi.ajp.2009.08121759] [PMID: 19570943]

[129] Shulgin, A. The continuation, 1997. *Available at: http://www.erowid.org/library/books_online/tihkal,* (Accessed August 12, 2016)

[130] Schultes, R.E. The plant kingdom and hallucinogens. *Bull. Narc.,* **1970**, *22*, 25-51.

[131] Goutarel, R.; Gollnhofer, O.; Sillans, R. Pharmacodynamics and Therapeutic Applications of Iboga and Ibogaine. *Psyched Mono Essays.,* **1993**, *6*, 70-111.

[132] Alper, K.R.; Lotsof, H.S.; Frenken, G.M.; Luciano, D.J.; Bastiaans, J. Treatment of acute opioid withdrawal with ibogaine. *Am. J. Addict.,* **1999**, *8*(3), 234-242. [http://dx.doi.org/10.1080/105504999305848] [PMID: 10506904]

[133] Mash, D.C.; Kovera, C.A.; Pablo, J.; Tyndale, R.F.; Ervin, F.D.; Williams, I.C.; Singleton, E.G.; Mayor, M. Ibogaine: complex pharmacokinetics, concerns for safety, and preliminary efficacy measures. *Ann. N. Y. Acad. Sci.,* **2000**, *914*, 394-401. [http://dx.doi.org/10.1111/j.1749-6632.2000.tb05213.x] [PMID: 11085338]

[134] Maciulaitis, R.; Kontrimaviciute, V.; Bressolle, F.M.; Briedis, V. Ibogaine, an anti-addictive drug: pharmacology and time to go further in development. A narrative review. *Hum. Exp. Toxicol.,* **2008**, *27*(3), 181-194. [http://dx.doi.org/10.1177/0960327107087802] [PMID: 18650249]

[135] Berger, M.L.; Palangsuntikul, R.; Rebernik, P.; Wolschann, P.; Berner, H. Screening of 64 tryptamines at NMDA, 5-HT1A, and 5-HT2A receptors: a comparative binding and modeling study. *Curr. Med. Chem.,* **2012**, *19*(18), 3044-3057. [http://dx.doi.org/10.2174/092986712800672058] [PMID: 22519402]

[136] Bulling, S.; Schicker, K.; Zhang, Y.W.; Steinkellner, T.; Stockner, T.; Gruber, C.W.; Boehm, S.; Freissmuth, M.; Rudnick, G.; Sitte, H.H.; Sandtner, W. The mechanistic basis for noncompetitive ibogaine inhibition of serotonin and dopamine transporters. *J. Biol. Chem.,* **2012**, *287*(22), 18524-18534. [http://dx.doi.org/10.1074/jbc.M112.343681] [PMID: 22451652]

[137] Glick, S.D.; Maisonneuve, I.S. Mechanisms of antiaddictive actions of ibogaine. *Ann. N. Y. Acad. Sci.,* **1998**, *844*, 214-226. [http://dx.doi.org/10.1111/j.1749-6632.1998.tb08237.x] [PMID: 9668680]

[138] Antonio, T.; Childers, S.R.; Rothman, R.B.; Dersch, C.M.; King, C.; Kuehne, M.; Bornmann, W.G.; Eshleman, A.J.; Janowsky, A.;

Simon, E.R.; Reith, M.E.; Alper, K. Effect of Iboga alkaloids on μ-opioid receptor-coupled G protein activation. *PLoS One,* **2013**, *8*(10), e77262. [http://dx.doi.org/10.1371/journal.pone.0077262] [PMID: 24204784]

[139] *https://www.erowid.org/chemicals/ibogaine/ibogaine.shtml,* (Accessed 12 august 2016)

[140] Alper, K.R.; Stajić, M.; Gill, J.R. Fatalities temporally associated with the ingestion of ibogaine. *J. Forensic Sci.,* **2012**, *57*(2), 398-412. [http://dx.doi.org/10.1111/j.1556-4029.2011.02008.x] [PMID: 22268458]

[141] Maas, U.; Strubelt, S. Fatalities after taking ibogaine in addiction treatment could be related to sudden cardiac death caused by autonomic dysfunction. *Med. Hypotheses,* **2006**, *67*(4), 960-964. [http://dx.doi.org/10.1016/j.mehy.2006.02.050] [PMID: 16698188]

[142] Paling, F.P.; Andrews, L.M.; Valk, G.D.; Blom, H.J. Life-threatening complications of ibogaine: three case reports. *Neth. J. Med.,* **2012**, *70*(9), 422-424. [PMID: 23123541]

[143] Pleskovic, A.; Gorjup, V.; Brvar, M.; Kozelj, G. Ibogaine-associated ventricular tachyarrhythmias. *Clin. Toxicol. (Phila.),* **2012**, *50*(2), 157. [http://dx.doi.org/10.3109/15563650.2011.647031] [PMID: 22304378]

[144] Vlaanderen, L.; Martial, L.C.; Franssen, E.J.; van der Voort, P.H.; Oosterwerff, E.; Somsen, G.A. Cardiac arrest after ibogaine ingestion. *Clin. Toxicol. (Phila.),* **2014**, *52*(6), 642-643. [http://dx.doi.org/10.3109/15563650.2014.927477] [PMID: 24940646]

[145] Papadodima, S.A.; Dona, A.; Evaggelakos, C.I.; Goutas, N.; Athanaselis, S.A. Ibogaine related sudden death: a case report. *J. Forensic Leg. Med.,* **2013**, *20*(7), 809-811. [http://dx.doi.org/10.1016/j.jflm.2013.06.032] [PMID: 24112325]

[146] Jalal, S.; Daher, E.; Hilu, R. A case of death due to ibogaine use for heroin addiction: case report. *Am. J. Addict.,* **2013**, *22*(3), 302. [http://dx.doi.org/10.1111/j.1521-0391.2012.00330.x] [PMID: 23617876]