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Plant-derived hallucinogens: neuropharmacological properties and psychoactive mechanisms — a narrative review

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Abstract: Introduction: Natural hallucinogens have been known since ancient times and were widely used in religious, shamanic, and folk rituals, as well as in traditional medicine. These compounds originate from plants, animals, and fungi and exhibit considerable diversity. Different groups of substances vary in their mechanisms of action, receptor responses, effects induced, and therapeutic applications. Hallucinogens are misused worldwide to achieve specific sensations and altered states of consciousness; therefore, their investigation is necessary to assess safety and predict long-term consequences of abuse. Some of these substances demonstrate pharmacological potential and are currently being studied for their possible use in the treatment of various conditions, including anxiety disorders, depression, and pain. Recent studies also indicate their potential role in the treatment of neurodegenerative diseases. Due to their wide-ranging therapeutic applications, psychedelics have become the subject of increasing scientific interest.
Aim of the study: The aim of this review was to summarize the current literature on natural hallucinogens of plant origin, with particular emphasis on their biological activity and neuropharmacological properties. It also highlighted their potential for possible therapeutic use.
Methodology: The review was conducted using scientific databases such as PubMed and Google Scholar, as well as relevant textbooks. Keywords were searched in both English and Polish, including hallucinogens, plant-derived hallucinogens, substance abuse, toxicology. The literature reviewed covered the years 1998 to 2025.
Conclusions: Natural plant-derived hallucinogens exhibit substantial diversity in terms of psychostimulant effects, safety profiles, addictive potential, and therapeutic applicability. Their activity across multiple

neurotransmitter systems presents a promising avenue for the development of novel treatments for neuropsychiatric disorders. However, further in-depth research is required to fully elucidate their mechanisms of action, clinical efficacy, and potential adverse effects. Continued investigation into their therapeutic potential and clinical applications is essential.

Keywords: plant-derived hallucinogens, natural hallucinogens, drugs, toxicology, therapeutic potential, neurotransmitter pathway.

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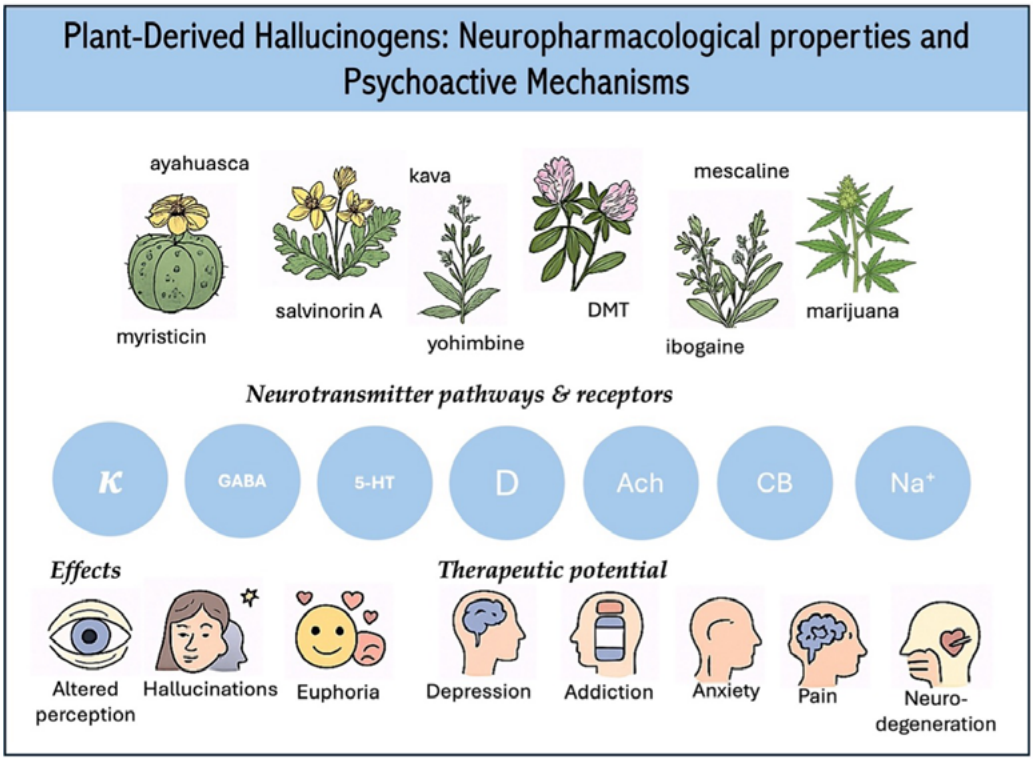

Sources of Hallucinogenic Substances

Hallucinogens are substances that affect the human body, particularly mood and emotional state. A hallmark of hallucinogen use is the occurrence of productive symptoms, such as hallucinations and illusions. Moreover, these substances impact cognitive functions, including concentration, memory as well as perception. In addition to these common effects, hallucinogens are attributed with more complex actions, such as distortion of time and space perception, personality changes, and altered understanding or interpretation of reality [1].

The effects of these compounds are often dose-dependent, in accordance with Paracelsus' 16th-century principle: *"All things are poison, and nothing is without poison. Only the dose makes*

a thing not a poison." For example, certain plants that contain hallucinogenic compounds may not influence brain function when consumed in small amounts insufficient to elicit pharmacological effects but may become psychoactive at higher doses.

Hallucinogens can be synthetic compounds, but a significant proportion of them are derived from natural sources. Natural hallucinogens can be obtained from various living organisms, including plants, animals, and fungi. These sources are widely distributed in nature. The term "natural hallucinogens" is often associated with exotic species found in remote areas, such as tropical regions. However, native flora and fauna, including species found in Poland, also harbor hallucinogenic compounds. Some plants commonly encountered in meadows and forests such as lupine (*Lupinus spp.*) or wormwood (*Artemisia absinthium*) contain substances with hallucinogenic potential [1, 2].

Although hallucinogens are now the subject of increasing scientific investigation, their use dates back to ancient times. Many were employed in religious rituals and tribal ceremonies. They were believed to possess healing properties, were used as poisons, and were often attributed with magical powers. Knowledge of their preparation was limited to a select few, as it was considered both secret and dangerous if misused. Thanks to modern chemistry and pharmacology, the structures and mechanisms of action of many hallucinogenic compounds have now been elucidated, enabling the potential development of some of these substances into therapeutic agents [1, 2].

On the other hand, it is important to acknowledge the role of hallucinogenic plants and fungi in the development of substance abuse. Their accessibility, increasing public knowledge, and the intense psychoactive effects they produce have contributed to a global rise in recreational use, particularly among young people.

Hallucinogens Derived from Plants

Hallucinogens Derived from Plants of the Solanaceae Family — Atropine, Scopolamine

The Solanaceae family of plants includes many species, but those most relevant toxicologically, particularly for their hallucinogenic properties, belong to the genera *Datura*, *Atropa*, *Hyoscyamus*, *Scopolia*, *Mandragora*, and *Brugmansia* [1, 2]. These plants, often part of local flora or cultivated ornamentally, are easily accessible and commonly used as narcotics. Their cultivation and possession remain legal [2].

Their psychoactive effects are mainly due to tropane alkaloids, atropine, scopolamine (hyoscine), and hyoscyamine, which act as muscarinic (M) receptor antagonists. These substances competitively block acetylcholine at presynaptic M_1 receptors in the CNS, leading to delirium, cognitive impairment, and hallucinations. Other muscarinic subtypes (M_2–M_5) are not significantly involved in this effect [3]. Tropane alkaloids also modulate serotonergic transmission: atropine and scopolamine are 5-HT_3 receptor antagonists, potentially affecting mood, memory, and emotional regulation via structures like the amygdala and hippocampus. These compounds induce both central and peripheral symptoms, including tachycardia, hypertension, dry mouth, mydriasis, hyperthermia, blurred vision, constipation, urinary retention, anxiety, agitation, incoherent speech, and misinterpretation of sensory stimuli. Users may experience paradoxical effects, ranging from euphoria to paranoia, and anterograde amnesia. Hallucinations are vivid and realistic, often mistaken for real events [2]. The severity of anticholinergic delirium can be rated on a 0–4 scale, from calm cooperation to coma and/or seizures [3]. These effects were historically exploited in criminal and

interrogation contexts, where atropine or scopolamine induced suggestibility and amnesia. Their mydriatic action was abused during torture, giving rise to the term "truth serum" [2].

Atropine and scopolamine are the most common agents in plant-derived hallucinogenic poisonings, implicated in up to 20% of deaths in this category [2]. Despite toxicity (lethal dose ca. 100 mg; death possible at lower doses in sensitive individuals) [2], both drugs have therapeutic uses: scopolamine for motion sickness and gastrointestinal spasm, atropine in ophthalmology, Parkinson's disease, and symptomatic bradycardia [2, 4].

Hallucinogens Derived from Hemp (Cannabis sativa) — Marijuana, Hashish

Cannabis sativa, commonly known as hemp, is native to Central Asia but is now cultivated globally. It has diverse industrial uses, including fiber production (for textiles, ropes, paper), oil extraction (for food and biofuel), pharmaceutical applications, animal feed (by-products), and birdseed. Medicinal use of cannabis dates back thousands of years, with anti-inflammatory, antiseptic, and anticonvulsant properties documented in ancient India and China [5].

Roughly 100 cannabinoids have been identified in cannabis, all sharing a 21-carbon terpenophenolic structure [5]. Key cannabinoids include Δ9-tetrahydrocannabinol (THC), cannabidiol (CBD), cannabinol (CBN) — a CBD degradation product, and cannabidiolic acid. Their concentrations vary based on plant chemotype and environmental factors.

Marijuana, a mixture of dried leaves and female inflorescences, typically contains 1–3% THC. Hashish, which is a resin extracted from female flowers, contains 5–10% THC and is classified as a narcotic. It induces euphoria, altered time and space perception, and sensory distortions [1, 6]. Marijuana remains the most commonly used illicit drug in the U.S. and is also widely used in Poland, with 10–20% of youth reporting use [6].

Cannabis products are usually smoked, yielding stronger psychoactive effects than oral intake [1]. After smoking, THC peaks in plasma within 6–10 minutes with 10–35% bioavailability; orally, it is only 4–12%. CBD also shows higher inhalation bioavailability (11–45%) than oral (approx. 6%) [5].

THC lacks a nitrogen atom (see Fig. 1) and acts as a partial agonist of CB_1 receptors, inhibiting cAMP synthesis and inducing hypolocomotion, catalepsy, analgesia, and hypothermia. It also activates CB_2 and PPARγ receptors (with neuroprotective and anti-inflammatory effects) and modulates TRP channels, particularly $TRPV_2$, with no effect on TRPV [7]. THC additionally affects dopaminergic, cholinergic, noradrenergic, serotonergic, and GABAergic systems. Mouse

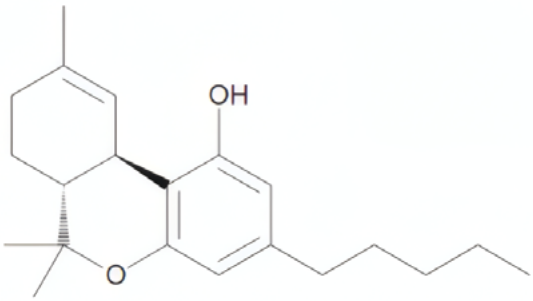

Fig. 1. THC structure.

models indicate that chronic THC exposure enhances hallucinogenic signaling via 5-HT_{2A} receptors through the Akt/mTOR/S6 pathway, shifting signaling from non-hallucinogenic to hallucinogenic mechanisms [8].

Its psychoactive effects include intensified sensory perception, emotional shifts, and altered cognition. Some users experience euphoria, while others report sedation or drowsiness. Cannabis over activates the endocannabinoid system, leading to neuropsychiatric symptoms [6]. Memory impairment is a notable effect, particularly among young users, and may lead to lasting cognitive deficits [6]. Cohort studies show that cannabis use between ages 12–18 significantly increases the risk of developing schizophrenia in early adulthood, even with infrequent use [9].

CBD, non-psychoactive, acts as an inverse agonist, antagonist, or negative allosteric modulator at CB_1 and CB_2 receptors, and also modulates GPR_{55}, TRP channels, PPARγ, dopamine D_2, 5-HT_{1A}, and $GABA_A$ receptors. These interactions contribute to its neuroprotective, antiepileptic, anxiolytic, antipsychotic, anti-inflammatory, analgesic, and anticancer potential [10]. CBD is already approved for treating epilepsy, including Lennox-Gastaut and Dravet syndromes, and is under investigation for its sedative and sleep-promoting properties [10].

Hallucinogens Derived from Salvia divinorum — Salvinorin A (Divinorin)

Salvia divinorum, known as "diviner's sage," is native to the forests of southwestern Mexico. While the precise origins of its use remain uncertain, it has likely been employed for centuries by Mazatec shamans for medicinal and divinatory purposes. Since the 1990s, it has gained popularity among adolescents and young adults as a recreational alternative to marijuana and LSD [11].

The plant's active compound, salvinorin A, is among the most potent natural hallucinogens, with effective doses as low as 250–500 μg [12]. Inhalation via smoking dried leaves or vaporizing extracts yields the fastest onset, with peak effects within 2 minutes, lasting 1–5 minutes and subsiding by 15–20 minutes [13]. Chewing fresh leaves produces effects within 5–10 minutes that may last 1–2 hours [14]. Oral ingestion of juice from fresh leaves generally results in milder effects due to gastrointestinal degradation of salvinorin A [14].

Salvinorin A exerts its effects through highly selective activation of kappa-opioid receptors (KORs). Uniquely, it is the first known KOR agonist lacking a nitrogen atom and the only naturally occurring non-alkaloid hallucinogen with a diterpenoid structure. These structural features contribute to both its potency and its potential in therapeutic KOR-targeted drug development [1]. Unlike classical psychedelics such as LSD or psilocybin, salvinorin A does not bind to 5-HT_{2A} receptors, but instead is classified as a dissociative hallucinogen, inducing perceptual distortions and a sense of detachment from self or surroundings [14].

In human studies, salvinorin A produced intense effects, including vestibular and interoceptive disturbances (e.g., altered spatial orientation, sensations of pressure), along with visions such as childhood memories, cartoon-like imagery, and encounters with entities. Doses up to 21 μg/kg did not affect heart rate or blood pressure [13].

Ayahuasca — Harmine, Harmaline, Tetrahydroharmine

Ayahuasca, also known by indigenous names such as *caapi*, *yaje*, *pinde*, *bakko*, *uipa*, *napa* and *shori*, is a traditional Amazonian brew made from the bark of *Banisteriopsis caapi* and the leaves of *Psychotria viridis* or *Diplopterys cabrerana*. Used for centuries in folk medicine as a purgative and emetic [1],

it has played a central role in shamanic healing and visionary rituals [15]. Archaeological evidence from a Mayan site in Naranjo (Guatemala) suggests ceremonial use as early as 2400 BCE [15].

The psychoactive effects of ayahuasca stem primarily from β-carboline alkaloids, harmine, harmaline, and tetrahydroharmine, from *B. caapi*, and N,N-dimethyltryptamine (DMT) from *P. viridis* [15, 16]. At low doses, the brew is sedative and euphoric. Higher doses induce hallucinations, often preceded by racing thoughts, laughter, and sensory disturbances [1]. DMT's hallucinogenic effects emerge about 40 minutes after ingestion, peak at 60–120 minutes, and last roughly 4 hours [15]. Users commonly report complex visuals, heightened introspection, and emotional processing, often described as "emotional healing" [15].

The ayahuasca experience typically unfolds in three phases: visual imagery with nausea or vomiting, spiritual encounters, and a final phase of fading visuals and fatigue. During the visual stage, users may perceive geometric patterns, intensified colors, or jungle animals, regardless of eye closure. The spiritual phase often features transcendental experiences, including encounters with plant and animal spirits, a sense of oneness with the universe, deep peace, ecstasy, and insights into death and the afterlife. Time perception is altered, with users experiencing timelessness, acceleration or deceleration of time, or time travel. Despite the intensity, users generally remain conscious and communicative [16].

DMT, structurally related to psilocybin, serotonin, and melatonin, interacts with 5-HT_{2A}, 5-HT_{2C}, and $mGluR_2$ receptors (16). Its oral activity depends on co-administered MAO inhibitors (MAOIs) from *B. caapi*, which prevent its degradation and allow systemic absorption. Harmine and harmaline act as reversible MAO-A inhibitors, while tetrahydroharmine functions as a weak serotonin reuptake inhibitor without MAOI activity [16]. β-carbolines alone can induce hallucinations, as observed in cases of intoxication with extracts from Syrian rue (*Peganum harmala*), which also contains similar alkaloids. Symptoms of intake include nausea, hallucinations, and agitation, linked to CNS stimulation and serotonergic effects [17]. β-carbolines, tricyclic indole alkaloids structurally akin to tryptamines, are under investigation for psychiatric applications due to their anxiolytic, sedative, and anticonvulsant properties [18]. Their mechanisms are believed to involve serotonin system modulation [15]. Harmine, the most abundant alkaloid in ayahuasca, has neuroprotective, anti-inflammatory, and antidepressant potential and supports astrocyte function and neural stem cell proliferation [15, 19]. It may also regulate GLT-1 and glutamine expression. Orally taken, harmine is hallucinogenic and more potent than tetrahydroharmine, which requires a dose nearly three times higher [15].

Harmaline was found to show anticancer, antimicrobial, and antiplatelet effects [20, 21] and demonstrates also antimalarial activity [22].

Hallucinogens Derived from Nutmeg (Myristica fragrans) — Myristicin

Nutmeg (*Myristica fragrans*) is a tree native to the Moluccas in Southeast Asia, producing seeds (nutmeg) and seed arils (mace), both commonly used as spices. Nutmeg contains up to 40% fat and 16% essential oil, rich in aromatic compounds, notably myristicin, which is chiefly responsible for its toxic and hallucinogenic properties [23]. Myristicin, a 1,3-benzodioxole derivative, is also present in cinnamon, parsley, carrots, and peppers, though at non-psychoactive levels [24]. Other derivatives in this essential oil include elemicin, safrole, and eugenol [25].

Historically, nutmeg has been used to treat gastrointestinal issues, nausea, diarrhea, and as a sedative [24]. High doses, typically 10–15 grams or ca. 400 mg myristicin, can cause neurological

effects. Myristicin and elemicin are thought to be metabolized into psychoactive amphetamines: MMDA and 3,4,5-trimethoxyamphetamine, respectively. Safrole may convert into MDA and MDMA through intermediate isomerization. These compounds act as 5-HT_{2A} receptor agonists, producing psychedelic effects [24, 26].

Despite its hallucinogenic potential, nutmeg is rarely used recreationally due to common adverse effects such as severe headaches [24]. Recreational use involves insufflation, smoking, or ingestion in beverages. Myristicin induces perceptual distortions, time-space disorientation, hallucinations, dissociation, and unrealistic sensations. Doses of 25–28 grams may result in anticholinergic poisoning, with symptoms as dry mouth, facial flushing, blurred vision, tachycardia, hypertension, agitation, and psychomotor restlessness appearing within 3–6 hours and lasting up to 72 hours [24].

Although not used clinically, myristicin shows pharmacological promise including anti-inflammatory, analgesic, antimicrobial, hepatoprotective, antioxidant, biocidal, and antiproliferative effects [27]. In vivo studies also suggest antidepressant activity comparable to imipramine. Thus, myristicin holds multidirectional therapeutic potential [24].

Ololiuhqui — Lysergic Acid Derivatives

Ololiuhqui and badoh negro are psychoactive preparations made from the seeds of climbing plants in the *Ipomoea*genus, native to Central and South America. Ololiuhqui is derived from *Ipomoea corymbosa* (formerly *Rivea corymbosa*), and badoh negro from *Ipomoea violacea.* Seeds are typically ground, macerated, or consumed as teas or beverages [1].

The seeds of *I. corymbosa* and *I. violacea* contain D-lysergic acid amide (LSA/ergine) and D-isolysergic acid amide (isoergine), which are structurally related to LSD, an ergot alkaloid [1]. Other alkaloids include elymoclavine and lysergol (hallucinogenic), as well as ergometrine and chanoclavine (non-hallucinogenic). These compounds are also found in *Argyreia nervosa* (Hawaiian baby woodrose), traditionally used in Hawaii as an aphrodisiac and intoxicant [28].

The psychoactive effects are primarily mediated through serotonergic system modulation, suggesting possible analgesic uses [29]. At higher doses, ololiuhqui can cause euphoria, frightening hallucinations, and psychosis [1]. A typical hallucinogenic dose requires 2–5 mg of ergine, which acts by inhibiting adenylate cyclase and reducing cAMP formation via dopamine D_2 receptor activation. Its effects, altered consciousness, hallucinations, disrupted wakefulness, are similar to LSD but 50–100 times weaker and lasting up to 4–8 hours. A. nervosa seed ingestion may cause serious psychiatric effects, including dissociation and schizophrenic relapse [28].

As of March 20, 2009, possession of Ipomoea corymbosa is prohibited under Polish drug laws [30].

Yopo and Cohoba — Tryptamine Derivatives

Yopo, cohoba, parica, and epena refer to psychoactive preparations made from the powdered seeds of Anadenanthera peregrina (formerly Piptadenia peregrina), traditionally used to alter consciousness and sensory perception. A related species, Anadenanthera colubrina, source of vilca, curupay, or cebil, has been similarly used for ritual and medicinal purposes. Native to South America, these trees have long been used by indigenous peoples in religious ceremonies. *A. colubrina* has also served in traditional medicine for treating respiratory ailments and promoting wound healing [31].

These preparations are typically administered via smoking or intranasal insufflation, inducing lightness, altered awareness, psychomotor stimulation, and enhanced sensory perception. Oral

use is generally ineffective due to MAO activity in the digestive tract. However, some preparations contain natural MAO inhibitors, allowing oral activity and hallucinogenic effects lasting 3–4 hours [1].

The primary active compounds are tryptamine derivatives DMT, *N-methyltryptamine* (NMT), *5-hydroxy-DMT* (5-OH-DMT, or bufotenin), and *5-methoxy-DMT* (5-MeO-DMT) (1). 5-OH-DMT is also present in toad *Bufo alvarius* venom, and 5-MeO-DMT is its metabolite. Both have strong hallucinogenic properties due to being an agonist at serotonin receptors 5-HT_{1A}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_3, and 5-HT_4, and are also potent serotonin releasers. NMT is a full 5-HT_{2A} receptor agonist, without affinity for 5-HT_{1A} receptors. It strongly promotes serotonin release, with milder effects on dopamine and norepinephrine. Orally inactive due to first-pass metabolism, NMT becomes psychoactive when vaporized (30–100 mg), producing effects for 45–70 minutes. When ingested with MAO inhibitors (50–180 mg), effects may last 2–5 hours [32].

Hallucinogens Derived from Piper methysticum — Kavalactones

Kava is a traditional beverage made from the roots of *Piper methysticum* (kava pepper), native to the western Pacific islands, including Micronesia and Vanuatu. It is typically consumed as an aqueous infusion and has been used for thousands of years for medicinal, recreational, and ceremonial purposes [33].

The psychoactive effects of kava are mainly due to kavalactones, including kavain, dihydrokavain, yangonin, methysticin, and dihydromethysticin, which make up 96% of the plant's lactone content [34, 35]. Other active components include flavokavains (A, B, C) and pinostrobin [35]. Kava is associated with anxiolytic, sedative, neuroprotective, and mood-enhancing effects, as well as improved sleep and cognitive function [1]. It is often compared to alcohol due to its relaxing properties and is generally considered safe when used in moderation [1]. Kava products have also been marketed for anxiety relief and weight loss [35].

Kava's psychoactive effects involve $GABA_A$, dopamine, opioid, serotonin, and histamine receptors [1]. Kavalactones enhance GABA transmission, inhibit voltage-gated ion channels, suppress norepinephrine reuptake, and reduce inflammation by blocking thromboxane A_2 synthesis. Specific kavalactones such as (+)-methysticin and (+)-kavain potentiate $GABA_A$ receptor activity by increasing chloride ion influx, though their mechanism differs from benzodiazepines. Kavain also inhibits Na^+ and L-type Ca^{2+} channels, reducing glutamate release [34].

It is important to note that the safety profile of kava-containing products has raised concerns due to reports of hepatotoxicity. Flavokavains, pipermethystine, or potential contamination with aflatoxins have been suggested as possible contributors to this adverse effect [35, 36].

Hallucinogens Derived from the Cactus Lophophora williamsii — Mescaline

Lophophora williamsii, commonly known as peyote, is a small, spineless cactus native to the deserts of the southern and southwestern United States. The name *peyotl* comes from Nahuatl, the language of the Aztecs, who used the cactus for over 5,500 years in ritual, religious, and medicinal contexts [37]. In traditional practices, fresh or dried buds (peyote buttons) are used to prepare decoctions or suspensions [1].

The main psychoactive compound in peyote is mescaline. A typical oral dose ranges from 200 to 400 mg of mescaline sulfate, equivalent to 3–6 buttons or 10–20 g of dried material [38]. The

strongest hallucinogenic effects appear 2–4 hours after ingestion, though peak effects may not coincide with peak plasma concentrations, suggesting that active metabolites may play a role [39]. Other compounds in peyote, such as pellotine, anhalonidine, and hordenine, may enhance mescaline's action.

Mescaline primarily acts through 5-HT_{2A} receptor activation, leading to intracellular calcium release. It also modulates 5-HT_{1A}, adrenergic, and dopaminergic pathways (39). Subjective effects include visual distortions, pseudo-hallucinations, heightened color perception, euphoria, and an enhanced mental state. However, adverse effects such as anxiety, panic, depressive episodes, or disturbing hallucinations may also occur. Physiological symptoms resemble sympathomimetic toxidrome and include mydriasis, hyperthermia, hyperreflexia, increased muscle tone, seizures, psychomotor agitation, ataxia, paresthesia, hypersalivation, hypertension, and tachycardia [40].

Hallucinogens Derived from Tabernanthe iboga — Ibogaine

Tabernanthe iboga is an evergreen shrub native to the tropical forests of Central and West Africa. Among indigenous groups, particularly the Bwiti people of Gabon, the root bark has traditionally been used in initiation rites and for spiritual communication with ancestors. Additionally, iboga is consumed as a mild stimulant and aphrodisiac [41]. The plant contains approximately 30 alkaloids, most notably ibogaine (24.6%), iboxygaine (11%), ibogaline (10.8%), and alloibogaine (8.2%), alongside minor constituents such as catharanthine, ibogamine, noribogaine, voacangine, and yohimbine [42].

Ibogaine and related alkaloids have been studied for their potential in treating substance use disorders, including addiction to opioids, alcohol, nicotine, and psychostimulants. Catharanthine also serves as a precursor to vinblastine, an antineoplastic agent [43]. Low doses (ca. 5 mg/kg b.w.) produce mild stimulant effects, while higher doses (20–30 mg/kg) induce intense, prolonged psychedelic experiences [44]. Doses exceeding 75 mg/kg in animal studies have shown neurotoxic effects, particularly degeneration of Purkinje cells in the cerebellum [45].

Ibogaine is primarily metabolized by CYP2D6 into noribogaine, an active metabolite that persists in the body for several days (45). Pharmacologically, ibogaine acts as an agonist at μ- and κ-opioid, 5-HT_{2A}, and 5-HT_3 receptors, and as an antagonist at NMDA and α3β4 nicotinic receptors. It also inhibits serotonin and dopamine reuptake (46), increases the expression of GDNF (43), and modulates transcription factors such as c-Fos and Egr-1 [46]. Noribogaine is a potent serotonin reuptake inhibitor and exhibits moderate κ- and weak μ-opioid receptor agonism. The hallucinogenic effects of ibogaine are likely mediated through 5-HT_{2A}, 5-HT_3, and σ_2 receptor activation [47].

The ibogaine experience is typically divided into two phases. The visionary phase (4–8 hours), often described as oneirophrenic, is marked by vivid dream-like imagery, rapid visual sequences, and enhanced autobiographical recall. Common symptoms include drowsiness, insomnia, dysesthesia, heightened auditory perception, dry mouth, nausea, sweating, tachycardia, and extrapyramidal signs such as ataxia, tremors, hyperreflexia, and clonus. The introspective phase (24–36 hours) features hypermnesia and deep psychological insight, with users frequently describing an improved ability to mentally organize personal experiences. Residual symptoms may include nausea, headache, insomnia, irritability, and mood fluctuations (commonly depressive, occasionally manic) [48].

Ibogaine has demonstrated efficacy in reducing cravings, alleviating withdrawal symptoms, and preventing relapse in individuals with substance use disorders. One proposed mechanism

involves inhibiting drug-induced dopamine release, thereby reducing the substance's rewarding effects. It is used in countries such as Mexico, where its legal status is unregulated. However, due to its potent and long-lasting hallucinogenic properties, ibogaine is banned in numerous countries, including the United States, Norway, Sweden, France, Belgium, Switzerland, the United Kingdom, and Italy [43]. In Poland, it was declared illegal under the Act of March 20, 2009. It remains available by prescription in Brazil and South Africa and is legal in New Zealand [49].

Despite its therapeutic promise, ibogaine's clinical use is constrained by cardiotoxicity. The compound blocks hERG potassium channels in cardiomyocytes, prolonging the QTc interval and potentially triggering life-threatening arrhythmias such as torsade de pointes, cardiac arrest, and sudden cardiac death. Several fatalities have been reported following unsupervised or improperly managed ibogaine administration [46, 50].

Summary

A broad range of plant-derived substances with hallucinogenic or psychoactive properties has been used traditionally for medicinal, ritualistic, or recreational purposes. Despite their diverse botanical origins and chemical classifications, many of these compounds act on shared neuropharmacological pathways, including especially serotonergic (5-HT_{2A}), dopaminergic, cholinergic, and opioid receptor systems, as well as ion channels involved in neuronal excitability.

In conclusion, while many of these natural compounds are associated with significant psychoactive effects and potential toxicities, they also present unique and underexplored opportunities for drug discovery. Their ethnopharmacological histories, combined with emerging preclinical data, highlight a need for systematic investigation into their mechanisms, efficacy, and safety in clinical settings. Responsible research into these substances may ultimately yield novel treatments for psychiatric, neurological, and substance-related disorders.

Founding

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