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The ethnobotany of psychoactive plant use: a phylogenetic perspective

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Psychoactive plants contain chemicals that presumably evolved as allelochemicals but target certain neuronal receptors when consumed by humans, altering perception, emotion and cognition. These plants have been used since ancient times as medicines and in the context of religious rituals for their various psychoactive effects (e.g., as hallucinogens, stimulants, sedatives, and aphrodisiacs). The ubiquity of psychoactive plants in various cultures motivates investigation of the commonalities among these plants, in which a phylogenetic framework may be insightful. A phylogeny of culturally diverse psychoactive plant taxa was constructed with their psychotropic effects and affected neurotransmitter systems mapped on the phylogeny. The phylogenetic distribution shows multiple evolutionary origins of psychoactive families. The plant families Myristicaceae (e.g. nutmeg), Papaveraceae (opium poppy), Cactaceae (peyote), Convolvulaceae (morning glory), Solanaceae (tobacco), Lamiaceae (mints), Apocynaceae (dogbane) have disproportionate number of psychoactive genera with various indigenous groups using geographically disparate members of these plant families for the same psychoactive effect, an example of cultural convergence. Pharmacological traits related to hallucinogenic and sedative potential are phylogenetically conserved within families, with unrelated families exerting similar psychoactive effects and affecting identical neurotransmitter systems (i.e. mechanistic convergence). However, pharmacological mechanisms for stimulant effects were varied even within families suggesting that stimulant chemicals may be more evolutionarily labile than those associated with hallucinogenic and sedative effects. Our study has shown that phylogenetic analyses of traditionally used psychoactive plants suggests multiple ethnobotanical origins and widespread human dependence on these plants for survival, motivating pharmacological investigation into their potential as modern therapeutics for various neurological disorders.

The ethnobotany of psychoactive plant use: a phylogenetic perspective

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Abstract

Psychoactive plants contain chemicals that presumably evolved as allelochemicals but target certain neuronal receptors when consumed by humans, altering perception, emotion and cognition. These plants have been used since ancient times as medicines and in the context of religious rituals for their various psychoactive effects (e.g., as hallucinogens, stimulants, sedatives, and aphrodisiacs). The ubiquity of psychoactive plants in various cultures motivates investigation of the commonalities among these plants, in which a phylogenetic framework may be insightful. A phylogeny of culturally diverse psychoactive plant taxa was constructed with their psychotropic effects and affected neurotransmitter systems mapped on the phylogeny. The phylogenetic distribution shows multiple evolutionary origins of psychoactive families. The plant families Myristicaceae (e.g. nutmeg), Papaveraceae (opium poppy), Cactaceae (peyote), Convolvulaceae (morning glory), Solanaceae (tobacco), Lamiaceae (mints), Apocynaceae (dogbane) have a disproportionate number of psychoactive genera with various indigenous groups using geographically disparate members of these plant families for the same psychoactive effect, an example of cultural convergence. Pharmacological traits related to hallucinogenic and

sedative potential are phylogenetically conserved within families. Unrelated families that exert similar psychoactive effects also modulate similar neurotransmitter systems (i.e. mechanistic convergence). However, pharmacological mechanisms for stimulant effects were varied even within families suggesting that stimulant chemicals may be more evolutionarily labile than those associated with hallucinogenic and sedative effects. Our study has shown that phylogenetic analyses of traditionally used psychoactive plants suggests multiple ethnobotanical origins and widespread human dependence on these plants for survival, motivating pharmacological investigation into their potential as modern therapeutics for various neurological disorders.

Keywords: drug discovery, ethnopharmacology, evolutionary ethnobiology, neuropsychopharmacology, psychotropic, traditional medicine

Introduction

Plants constantly evolve to produce various defensive secondary metabolites against their equally adaptive predators (Polya, 2003; Wink, 2003). Some well-known psychoactive compounds such as atropine, caffeine, cocaine, nicotine and morphine are believed to have been products of this evolutionary arms race (Howe & Jander, 2008; Fürstenberg-Hägg, Zagrobelny, & Bak, 2013). Psychoactive, alternatively psychotropic, substances act on the nervous system affecting mental processes and behavior (Spinella, 2001; Rätsch, 2005). They include hallucinogens that distort reality, sedatives/narcotics that induce sleep, calmative or anxiolytics, antidepressants, stimulants that wake the mind, and even aphrodisiacs that promote sexual arousal. Interestingly, humans have exploited alternate uses for plants containing psychoactive phytochemicals that have purportedly evolved to ward off plant predators. However, the affinity

of these phytochemicals within the hominid nervous system may also indicate some kind of mutualistic co-evolution, with ancient humans seeking and perhaps cultivating plant psychotropics to facilitate survival, by alleviating starvation, fatigue and pain (Sullivan & Hagen, 2002).

Psychoactive compounds have specific molecular targets in the nervous system, and interact in a particular way with neuronal receptors to produce various psychoactive effects (Spinella, 2001; Polya, 2003). For instance, morphine in opium poppy (*Papaver somniferum,* Papaveraceae) eliminates pain by binding to opioid receptors (Polya, 2003), but simultaneously promotes sedation and euphoria, by disinhibiting dopamine-containing neurons in the limbic system (Johnson & North, 1992). Dopamine is ultimately responsible for feelings of elation and satisfaction, which occur after some rewarding act like sex or food satiety. Addiction arises from wanting to re-experience the pleasure due to the drug's ability to cause dopamine buildup (Lüscher and Ungless, 2006). Compounds that mimic serotonin and act as receptor agonists like mescaline in the peyote cactus (*Lophophora williamsii,* Cactaceae*),* trigger hallucinations and cognitive breakdown (Polya, 2003). Stimulating substances, such as the alkaloid nicotine in tobacco, *Nicotiana tabacum* (Solanaceae), mimic the endogenous neurotransmitter acetylcholine stimulating muscle contractions and cholinergic areas of the brain involved in arousal and attention (Polya, 2003). And yet, the confamilial *Atropa belladonna*, contains a chemically different alkaloid, atropine, which promotes sedation and incapacitation via its action as muscarinic acetylcholine antagonist, blocking neuromuscular communication (Spinella, 2001).

It is well established that all cultures, ancient or modern, have some kind of drug culture, relying on psychoactives for recreational, ritual and/or medicinal uses (Schultes, 1976; Schultes, Hofmann & Rätsch, 1998; Rätsch, 2005). Shamanistic religions have existed in the Old World

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of Europe, Asia and Africa, believing that psychoactive plants are capable of healing through divine power. Marijuana (*Cannabis* spp., Cannabaceae) and opium poppy are among the most popular psychoactive plants used by Old World shamans. Marijuana was used in ancient China for various afflictions like malaria and constipation, and even as a narcotic in surgeries. In India, the plant was considered sacred promoting pleasurable sensations in the user (Clarke & Merlin, 2013). Tetrahydrocannabinol (THC) in marijuana, exerts these actions by binding to cannabinoid receptors, mediating sensory pleasure (Mahler, Smith & Berridge, 2007). Another familiar psychoactive, opium poppy was used for medicinal and recreational purposes. It probably originated in the Mediterranean, but widespread use has confounded its evolutionary origin (Merlin, 2003). It was recorded in the Eber papyrus, an ancient Egyptian scroll, that opium poppy was used to stop the excessive crying of children (Vetulani, 2001). The plant contains morphine and codeine that are responsible for its hypnotic and analgesic properties (Heinrich et al., 2012).

Indigenous people of the New World have also used psychotropic substances, including tobacco, ayahuasca, and coca, even more so than cultures of the Old World (Schultes, 1976). Tobacco from the leaves of *N. tabacum* has long been used in the Americas, with cultivation in pre-Columbian Mexico or Peru (Rätsch, 2005). American Indians believed in the medicinal power of tobacco, and it was smoked in ceremonial peace pipes to seal covenants. In the Amazon Basin of South America, the hallucinogenic beverage, ayahuasca, is made by healers from the boiled crushed stems of the caapi, *Banisteropsis caapi* (Malpighiaceae), along with the leaves of chacruna, *Psychotria viridis* (Rubiaceae). Chacruna contains serotonergic N,N-dimethyltryptamine (DMT), that is activated by the beta-carbolines in caapi (McKenna, 1996). In the Andes, indigenous peoples chew coca leaves of *Erythroxylum coca* (Erythroxylaceae) to

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cope with hard labor, removing symptoms of fatigue and hunger (Nigg & Seigler, 2013). Its cocaine content prevents dopamine reuptake producing increased energy and mood elevation (Spinella, 2001).

The ubiquity of psychoactive plants in various cultures motivates investigation of the commonalities among these plants, in which a phylogenetic framework may be insightful. Information is assigned to nodes of the phylogeny, instead of one species at a time, facilitating the study of trait distributions (Saslis-Lagoudakis et al., 2015). Phylogenetic studies of culturally diverse medicinal plants have repeatedly shown that medicinal uses and phytochemical traits are not randomly distributed on the phylogeny, but are shared by closely related plants, regardless of these plants' cultural and geographic designations (Saslis-Lagoudakis et al., 2012; Saslis-Lagoudakis et al., 2015; Xavier & Molina, 2016). In this study we aimed to understand if there is a similar pattern of cultural convergence (Xavier & Molina, 2016) in psychoactive plants using phylogenetic analysis—does the phylogeny of culturally important psychoactive plants reveal a preference for certain plant families and for specific psychoactive effects (hallucinogenic, sedative, stimulant, etc.)? Additionally, we sought to understand if there is also a pattern of mechanistic convergence, such that unrelated plants with similar psychoactive effects ultimately affect similar neurotransmitter systems. Our study provides insight into the ethnobotanical origins of psychoactive plant use and suggests new plant sources of psychopharmacological drugs

Materials and **Methods**

Pyschoactive taxa of seed plants (126 genera) used by various indigenous groups were compiled for this study (Table 1), but plants with psychoactive uses only after alcoholic

fermentation were excluded (e.g., wine from grapes, *Vitis vinifera*). Congeneric species were only represented once in the phylogeny, e.g., *Datura* spp. included *D. discolor* Bernh., *D. ferox* L., *D. innoxia* Mill., *D. metel* L., *D. stramonium* L., *D. wrightii* Regel. This is to account for taxonomic uncertainties that are common in species circumscriptions, and also not to visually bias the phylogeny towards a certain family with multi-species genera (e.g., *Datura)*. The plants' names were verified in the Plant List (2013), a working list of all known plant species that is maintained by the Royal Botanic Gardens and the Missouri Botanical Garden. The psychoactive uses of each plant were categorized as follows: hallucinogen, sedative (=narcotic/hynotic), stimulant, anxiolytic (=relaxant), and antidepressant. As psychotropic plants may also exert analgesia and/or aphrodisiac effects, these effects were additionally determined for each plant. Multiple effects based on literature were not uncommon. Thus, plants were assigned multiple psychoactive attributes, if applicable. For congeneric taxa, uses for each species were all noted.

The 126 psychoactive plant taxa were categorized according to the ethnic groups they were associated with: Native American (including North, Central and South America, 49 genera), European (15), Temperate Asian (including China, Russia, 10), Middle Eastern and African (19), Indomalayan (including India and Southeast Asia, 10), Australasia (including Australia, New Guinea, New Zealand, Pacific Islands, 4). Taxa with traditional psychoactive uses in at least two of these groups were designated multi-cultural (19). The uses of the plants were based on the originating indigenous cultures. For example, harmal, *Peganum harmala* (Nitrariaceae), is native in the Mediterranean (Europe), but it was used as a stimulant in the Middle East and in Africa, so harmal was assigned to the latter. Guava, *Psidium guajava* (Myrtaceae), is native to tropical America, but was only used as psychoactive in Africa (Rätsch, 2005). *Argyreia nervosa* (=*A. speciosa*), though of Indian origin, is considered multi-cultural

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here. It has been used in Ayurvedic medicine as an analgesic and aphrodisiac (Galani, Patel & Patel, 2010), but Hawaiians (Australasia) have been using it as alternative to marijuana (Rätsch, 2005). Cultural designations for each plant were all noted, with overlapping origins, if applicable, indicated.

To construct the phylogeny, the sequence of *rbcL* (the gene that codes for the photosynthetic enzyme rubisco; Clegg, 1993) for each psychoactive plant taxon was obtained from GenBank database http://www.ncbi.nlm.nih.gov/genbank using BLASTN (e-value=0, query coverage >50%; Altschul et al., 1990). If there are multiple species within the genus, only the genus name was indicated. The *rbcL* sequences were not available in GenBank for the following species: *Calea ternifolia, Calliandra anomala*, *Crocus sativus, Horsfieldia asutraliana, Iochroma fuchsioides*, *Juniperus recurva, Justicia pectoralis, Lactuca virosa, Ledum palustre, Lonchocarpus violaceus, Nymphaea ampla, Pachycerus pectenaboriginum, Psychotria viridis, Ptychopetalum olacoides, Psidium guajava, Rhynchosia pyramidalis, Sassafras albidum, Sceletium tortuosum, Tanaecium nocturnum, Tilia tomentosa, Urtica urens, Veratrum album,* and *Virola elongata*. In these cases, the *rbcL* sequence for any species within the corresponding genus was downloaded instead.

The *rbcL* sequences of the psychoactive plants were aligned using default parameters in MAFFT v.7 (Katoh & Standley, 2013). PhyML (Guindon & Gascuel, 2003) was utilized to reconstruct the phylogeny applying the general time reversible (GTR) DNA model (Tavaré, 1986) with aLRT (approximate likelihood ratio test) Shimodaira-Hasegawa-like (SH-like) branch support (Simmons & Norton, 2014) and 100 bootstrap replicates. ITOL (Interactive Tree of Life, www.itol.embl.de), a web-based tool used for the display and manipulation of phylogenetic trees (Letunic & Bork, 2006), was used to highlight and map the traits in Table 1

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(indigenous culture, psychoactive uses). Affected neurotransmitter (NT) systems (Table 2) for the main psychoactive families were also added to the phylogeny. Cosmetic editing of the ITOL results was completed in Adobe Illustrator CS4.

Results

The 126 psychoactive seed plant taxa belong to 56 families and 31 orders (Table 1) and together comprise 1.6% of the total generic diversity for these families. The phylogeny reflects expected relationships (Angiosperm Phylogeny Group/APG IV, 2016). Within eudicots there seems to be cultural bias of psychotropic use toward asterid members (61) vs. rosids (31). Nonetheless, the scattered distribution of psychoactive taxa throughout the angiosperm phylogeny suggests that psychoactive phytochemicals have evolved multiple times throughout angiosperm evolution. However, certain families are more diverse with at least 3 or more genera: Myristicaceae, Papaveraceae, Malvaceae, Fabaceae, Cactaceae, Asteraceae, Convolvulaceae, Solanaceae, Lamiaceae, Rubiaceae, Apocynaceae. However, psychoactive diversity within these families may be positively correlated with the family's generic diversity. To test this, a Pearson's product moment correlation coefficient was calculated to test the relationship between the number of psychoactive genera in our study versus the generic diversity of each family (from Christenhusz & Byng, 2016). Taxonomically diverse families like Asteraceae and Rubiaceae (>500 genera each) did not always have proportionally higher number of psychoactive genera with the correlation coefficient very weakly positive ($r = 0.004$). However, Myristicaceae (4 psychoactive genera out of 21 total), Papaveraceae (4/42), Cactaceae (5/127), Convolvulaceae (4/53), Solanaceae (16/100), Lamiaceae (8/241), Apocynaceae (7/366) have a disproportionate number (>1.6%) of their family's generic diversity psychoactive. We focused on the neurotransmitter systems affected by psychotropic members of these families as well as

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185 psychoactive members in the inherently diverse families of Fabaceae, Malvaceae, Rubiaceae,
186 and Asteraceae (Fig. 1).

187 Unrelated families may exert similar psychoactive effects (Fig. 1). Cactaceae, Fabaceae,
188 Myristicaceae, Convolvulaceae, and Solanaceae are mainly hallucinogens, though they are
189 unrelated. Of the 5 cultural groups, Native Americans have traditionally used the most
190 psychoactives (49/126) with predilection for hallucinogens (Fig. 2) in Cactaceae, Fabaceae,
191 Convolvulaceae. These families mainly work as serotonin receptor agonists (Fig. 1; Table 2), the
192 same mechanism as hallucinogenic Myristicaceae that has been used in Australasia and
193 Indomalaya. Members of Solanaceae have also been used as hallucinogens, predominantly by
194 Native Americans and Europeans, but act via a different mechanism—as acetylcholine
195 antagonists. Hallucinogenic asterids are also often used as aphrodisiacs (16/30=53% vs.
196 4/18=22% hallucinogenic rosids).

197 The unrelated Papaveraceae and Lamiaceae similarly show sedative/narcotic qualities,
198 another popular psychoactive effect among different cultural groups (Fig. 2). However, they
199 affect different neurotransmitter systems with Papaveraceae working mainly as opioid receptor
200 agonists. Lamiaceae work as receptor agonists of gamma-amino butyric acid (GABA), which
201 also mediates the family's anxiolytic effects. Psychoactive members of these families also tend
202 to exhibit analgesic effects.

203 Plants with anxiolytic and antidepressant properties are relatively sparse (Fig. 1, 2), with
204 Europeans showing slightly increased use of these plants. Members of Apocynaceae and
205 Rubiaceae that show an antidepressant effect facilitate this effect by increasing synaptic levels of
206 monoamine neurotransmitters (serotonin, dopamine, noradrenaline; Fig. 1; Table 2). In contrast,
207 plants with stimulating effects are numerous and randomly distributed throughout the phylogeny,

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exhibiting varying mechanisms of action (see Malvaceae and Rubiaceae, Fig. 1; Table 2).

Discussion

The phylogenetic distribution of psychoactive plants shows multiple evolutionary origins and provides evidence for the adaptive benefit of phytochemicals that are psychoactive in animals. It has been hypothesized that mammals may have sought plants with these phytochemicals that were chemically similar to endogenous neurotransmitters to augment their nutrition, as well as to facilitate survival, alleviating pain and hunger (Sullivan & Hagen, 2002). Whether this phylogenetic distribution, showing multiple independent origins of psychoactive plants, is due to co-evolutionary mutualism with animals remains to be tested. However, it is clear that certain psychoactive effects are concentrated in certain groups, which demonstrates that psychoactive phytochemicals are phylogenetically clustered. Phylogenetic clustering of medicinal traits has also been revealed in other studies (Saslis-Lagoudakis et al., 2012; Saslis-Lagoudakis et al., 2015; Xavier & Molina, 2016).

In the phylogeny, 11 of 56 plant families have more psychoactive genera (3 or more) compared to others. Accounting for these families' total generic diversity shows that Myristicaceae, Papveraceae, Cactaceae, Convolvulaceae, Solanaceae, Lamiaceae, and Apocynaceae have a disproportionate number of psychoactive genera. The psychoactive diversity of the other families, Fabaceae, Malvaceae, Asteraceae, and Rubiaceae, may be an artifact of their overall higher generic diversity. Nonetheless, we see a pattern where these plant families are being used for similar psychoactive applications by different cultures, a pattern of cultural convergence (Xavier & Molina, 2016) with bias, interestingly, for plants with hallucinogenic and sedative/narcotic potential.

231

232 ***Pharmacology of hallucinogenic plants***. The use of hallucinogens is widespread in
233 cultures which assigned positive meaning to the experienced altered state of consciousness, such
234 as allowing the user access to the spiritual world (Júnior et al., 2015). Hallucinogens used in
235 divination and religious healing (i.e. entheogens) may have played a significant role in human
236 evolution (Schultes, Hofmann & Rätsch, 1998). Native Americans prolifically used
237 hallucinogens, but hallucinogenic use seems to be lower in temperate Asia. Increased
238 hallucinogenic use among indigenous peoples of Brazil (South America) was also reported by
239 Rodrigues & Carlini (2006).
240 In our study we find hallucinogenic plants in Myristicaceae, Fabaceae, Cactaceae, and
241 Convolvulaceae mainly acting as serotonin receptor agonists, a case of mechanistic convergence
242 where unrelated families exert the same psychoactive effect by affecting identical
243 neurotransmitter systems. Mescaline is the serotonergic chemical in Cactaceae, while DMT
244 (N,N-dimethyltryptamine) and bufotenin (Polya, 2003) have the same effect and evolved
245 independently in hallucinogenic taxa in Fabaceae. Serotonin itself occurs in fabaceous *Mucuna*
246 *pruriens* (Polya, 2003), a hallucinogen and aphrodisiac in Ayurvedic medicine (Lampariello et
247 al., 2012). DMT also exists in *Virola* of the unrelated Myristicaceae (Polya, 2003), and the
248 alkaloid, elemicine, in confamilial *Myristica fragrans* transforms into a mescaline-like molecule
249 (Rätsch, 2005). The unrelated Convolvulaceae exerts hallucinogenic effects possibly through its
250 ergot alkaloids that work also as serotonin receptor agonists (Polya, 2003; Kennedy, 2014).
251 However, hallucinogenic taxa in the closely related Solanaceae may work on a different
252 mechanism. Its tropane alkaloids such as scopolamine and atropine act as muscarinic receptor
253 antagonists, inhibiting acetylcholine transmission (Spinella, 2001). Interestingly, in another

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asterid member, *Salvia divinorum* (Lamiaceae), the diterpene, salvinorin A, possibly works as a hallucinogen through its action on specific opioid receptors (kappa) (Willmore-Fordham et al., 2007), the same receptor modulated by the alkaloid ibogaine in hallucinogenic *Tabernanthe iboga* (Apocynaceae; Spinella, 2001). Various unrelated taxa seemingly achieve their hallucinogenic effects by modulating serotonin, acetylcholine, and/or endogenous opioids.

It is interesting that in many hallucinogenic asterids, aphrodisiac effects are quite common (see Asteraceae, Solanaceae, Apocynaceae). In members of Solanaceae this effect may be due to dopamine increase from cholinergic antagonism (Spinella, 2001). Dopamine is important in sexual arousal and orgasm (Krüger, Hartmann & Schedlowski, 2005). This neurotransmitter is also modulated by ibogaine in *T. iboga* (Wells, Lopez & Tanaka, 1999), which is also traditionally used as an aphrodisiac along with other Apocynaceae members. In another asterid family, Asteraceae, it is not clear which of its phytochemical constituents produce psychoactive effects, except perhaps for wormwood (*Artemisia* spp.) wherein the monoterpenoid, thujone, antagonizes the main inhibitory neurotransmitter, gamma-aminobutyric acid (GABA), resulting in its stimulant, almost convulsant, effects (Höld et al., 2000). However, the great diversity of sesquiterpene lactones prevalent in the family (Chadwick et al., 2013) are likely implicated in its hallucinogenic and aphrodisiac potential (Fig. 1; Table 2). These findings motivate further research into these asterid families as new therapeutics for sexual dysfunction.

Pharmacology of plants with sedative and analgesic effects. Dr. W. E. Dixon, well-known British pharmacologist of his time, once commented that narcotic indulgences reflect the sad paradox that humans seemed to get their "chief pleasures in life by escaping out of life" (Narcotic plants, 1928: 252). There may be truth to this as narcotic/sedative effects were commonly sought for by various cultures, second to hallucinogens, with members of

277 Papaveraceae and Lamiaceae traditionally used for this purpose. Opium poppy of Papaveraceae
278 has long been known to ancient Greeks and Sumerians and is considered one of the most
279 important medicinal plants in history. Its opium latex is the source of >30 alkaloids including
280 morphine and codeine, which bind to opioid receptors, promoting sedation and analgesia
281 (Heinrich et al., 2012). Though there are other members of Papaveraceae that have been used by
282 Asians and Native Americans for sedation and pain relief (Rolland et al., 1991; Brahmachari,
283 Gorai & Roy, 2013; Shang et al., 2015), the substances responsible for their effects are not well
284 characterized as in opium poppy, but it is possible that their effects are also mediated via opioid
285 receptors (Shang et al., 2015) and at least in *Eschscholzia californica* (California poppy) via the
286 GABAergic system (Fedurco et al. 2015).

287 In asterids, sedation is produced by members of Solanaceae and Lamiaceae possibly via
288 different pathways. Tropane alkaloids in Solanaceae, particularly scopolamine, promote sedation
289 through depression of the central nervous system resulting from anticholinergic activity (Renner,
290 Oertel, & Kirch 2005). In Lamiaceae, this effect is mainly facilitated via the GABAergic
291 pathway (Shi et al., 2014), with leonurine (Rauwald et al., 2015) and essential oil components
292 (Lis-Balchin & Hart, 1999; Awad et al., 2009; Shi et al., 2014; Ferlemi et al. 2015) as the
293 primary chemicals that increase GABA. Coincidentally, Lamiaceae members also possess
294 analgesic effects, but the pharmacology is unclear (Hajhashemi, Ghannadi & Sharif, 2003;
295 Dobetsberger & Buchbauer, 2011) and may reflect the antinociceptive properties of activation of
296 GABA receptors (Enna & McCarson, 2006). *Salvia divinorum,* however, does not contain
297 essential oils (Rätsch, 2005), but has been pharmacologically shown to exert analgesic quality
298 through activation of the same opioid receptors (kappa) implicated in its hallucinogenic effect
299 (Willmore-Fordham et al., 2007), a mechanism different from the other Lamiaceae species here.

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Some members of the distantly related Rubiaceae, including *Psychotria colorata* (Elisabetsky et al., 1995) and *Mitragyna speciosa* (Suhaimi et al., 2016), have also shown similar opiate-like antinociceptive properties, confirming their traditional uses. Repeated evolution of phytochemicals with affinity for animal opioid receptors may imply some adaptive benefit to plants.

Pharmacology of plants with anxiolytic and antidepressant effects. The relatively sparse distribution of anxiolytic and antidepressant plants in the phylogeny compared to hallucinogens and sedatives, suggests that there is less cultural [illegible]lity for plants with these psychoactive properties. In the US there is a cultural aspect to the pathogenesis of anxiety and depression with minority groups reporting lower incidence compared to whites (Hofmann, Asnaani & Hinton, 2010). The definition itself of depression is wrought with Western assumptions of individual happiness, which is in contrast to other cultures' view of happiness arising from social interdependence (Chentsova-Dutton, Ryder & Tsai, 2014). This may explain why these psychoactive uses were less prevalent compared to hallucinogenic, stimulant and sedative applications. The observed pattern that Europeans seem to use plants with anxiolytic and antidepressant effects more so than the other groups may be reflective of this Western notion of happiness.

Sedative members of Lamiaceae often possess anxiolytic qualities (Fig. 1), and this is probably due to overlapping effects on GABA (Tallman et al., 2002). Phytol, an alcohol in essential oils (Costa et al., 2014) has been shown to increase GABA. Rosmarinic acid in rosemary *(R. officinalis)* and lemon balm *(M. officinalis),* both Lamiaceae, also works as GABA transaminase inhibitor preventing GABA catabolism (Awad et al., 2009).

322 In members of Apocynaceae and Rubiaceae (Gentianales) that show anxiolytic and
323 antidepressant effects, another mechanism may be involved. *Rauvolfia serpentina*
324 (Apocynaceae) is used in Ayurvedic medicine to treat depression (Mamedov, 2005). In Africa,
325 the confamilial *T. iboga* is used as a stimulant to combat fatigue and hunger, but may have
326 potential in easing depressive symptoms (Nigg and Seigler, 2013). *Pausinystalia yohimbe*
327 (Rubiaceae) has stimulating effects on the nervous system and has been used to increase libido
328 by men in central Africa (Rätsch, 2005). The confamilial *M. speciosa* has also been used as
329 stimulant to counteract fatigue and increase endurance for work in Southeast Asia (Idayu et al.,
330 2011) The main chemical constituents of these closely related families are indole alkaloids that
331 generally increase synaptic levels of the monoamine neurotransmitters, serotonin, dopamine and
332 noradrenaline by various mechanisms including inhibition of transport and reuptake (Wells,
333 Lopez & and Tanaka, 1999; Zheng, Fan & Liu, 2013; Kennedy, 2014). The unrelated but
334 popular herbal antidepressant, St. John's wort (*Hypericum perforatum*, Hypericaceae; Spinella,
335 2001), as well as pharmaceutical antidepressants, produces its effects (Feighner, 1999) via the
336 same mechanism of reuptake inhibition.
337 Monoamine transport inhibitors may be rife in Apocynaceae (or Gentianales). In their
338 ethnopharmacological studies in South Africa, Heinrich & Jäger (2015) also discovered two
339 other Apocynaceae species that exhibited high affinity to the serotonin transporter. Interestingly,
340 these plants were also being used by traditional healers to treat those who were "being put down
341 by the spirits". A primary side effect of many conventional antidepressants is sexual dysfunction
342 (Higgins, Nash, & Lynch, 2010), which seems to contradict the aphrodisiac effect exhibited by
343 *T. iboga* and *P. yohimbe*, in addition to their antidepressant effects. This suggests that members

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344 of Gentianales may be exploited as novel pharmaceuticals for depression without the known side
345 effects of sexual dysfunction.

346 ***Pharmacology of plants with stimulating effects.*** Plants traditionally used as stimulants
347 are numerous and scattered throughout the phylogeny, indicating that stimulant phytochemicals
348 have evolved multiple times independently in different lineages and may confer some
349 evolutionary benefit. A few display paradoxical effects as both stimulating and sedating, such as
350 marijuana (Block et al., 1998) and *M. speciosa* (Rätsch, 2005), which may be attributed to
351 dosage, idiosyncrasies, or antagonistic phytochemicals.

352 Albeit belonging to diverse families, coffee (*Coffea arabica*, Rubiaceae), yerba mate (*Ilex*
353 *paraguariensis*, Aquifoliaceae), kola (*Cola* spp., Malvaceae), tea (*Camellia sinensis*, Theaceae),
354 and guarana (*Paullinia cupana*, Sapindaceae), all contain caffeine, a xanthine alkaloid, which
355 acts as a stimulant through antagonism of adenosine receptors, interfering with the binding of the
356 inhibitory endogenous adenosine (Rätsch, 2005). Yohimbe (*P. yohimbe*), though confamilial
357 with coffee, contains the indole alkaloid, yohimbine, which binds to adrenergic and serotonin
358 receptors (Polya, 2003), and is structurally and mechanistically similar to other stimulant
359 alkaloids found in diverse plant groups such as ergot alkaloids in Convolvulaceae, ibogaine in *T.*
360 *iboga* and *Voacanga* sp. (Apocynaceae), and harmaline in *Peganum harmala* (Nitrariaceae)
361 (Polya, 2003).

362 Within the same family, particularly Solanaceae, contrasting effects and mechanisms may
363 also be observed. Though many solanaceous members contain tropane alkaloids that work as
364 anticholinergic hallucinogens with incapacitating effects, tobacco exerts stimulant activity
365 through an opposite mechanism, with nicotine, a pyrrolidine alkaloid, promoting acetylcholine
366 transmission. However, tropane alkaloids are not unique to Solanaceae. Cocaine, found in the

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unrelated *E. coca* (Erythroxylaceae), suggests that chemically similar alkaloids may evolve in divergent lineages. This is also exemplified in the gymnosperm *Ephedra* spp. (Ephedraceae; Polya, 2003) and the unrelated angiosperms *Sida acuta* (Malvaceae) and *Catha edulis* (Celastraceae), which all possess ephedrine, a phenethylamine that mimics noradrenaline, stimulating the adrenergic receptor system (Prakash, Varma & Gosal 1998; Polya, 2003; Rätsch, 2005), and thus the sympathetic nervous system responsible for the "fight-and-flight" response.

It is notable that, even within the same family, the stimulant phytochemicals are chemically diverse. This phylogenetic pattern may indicate that stimulant chemicals may be more evolutionarily labile than hallucinogenic and sedative phytochemicals that seem to be more phylogenetically conserved within the family. As to why this is begs further inquiry, but hints at the evolutionary benefits of these chemically diverse plant psychoactive compounds that have evolved multiple times among seed plants, possibly with multifarious roles other than to function solely as allelochemicals.

Conclusion

Phylogenetic analysis has demonstrated multiple evolutionary origins of traditionally used psychoactive plant groups. Whether this pattern is due to repeated co-evolutionary mutualism with animals remains to be tested. Psychoactive diversity of some highlighted families is probably due to the inherent elevated diversity in these families. However, other plant families have a disproportionate number of psychoactive genera, and their phytochemical and psychoactive traits show phylogenetic clustering, with different cultures converging on geographically-disparate members of these families for similar uses: Myristicaceae, Cactaceae, Convolvulaceae, and Solanaceae as hallucinogens; Papaveraceae, Lamiaceae for analgesia and

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sedation; Apocynaceae for antidepressant effects. In certain unrelated families with the same psychoactive effect, the same neurotransmitter systems were also affected, i.e., mechanistic convergence. However, this was not the case for plants with stimulant effects, where confamilial taxa possess chemically diverse stimulant alkaloids, and chemically similar stimulant alkaloids exist in diverse lineages. Nonetheless, our findings suggest that the majority of traditionally used psychoactive plants generally display phylogenetic conservatism in phytochemistry and pharmacology, and may be explored as novel therapeutics for neurological disorders such as depression, anxiety, pain, insomnia and sexual dysfunction, reinforcing the potential of plant psychoactives as "springboards for psychotherapeutic drug discovery" (McKenna, 1996).

ACKNOWLEDGMENTS

This research was conceived as part of NA's MSc thesis, and we are grateful to the King Abdullah scholarship program (of Saudi Arabia) and to NA's family for various forms of support. We also thank Joseph Morin and Timothy Leslie for reviewing earlier drafts of this manuscript.

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753 **FIGURES**

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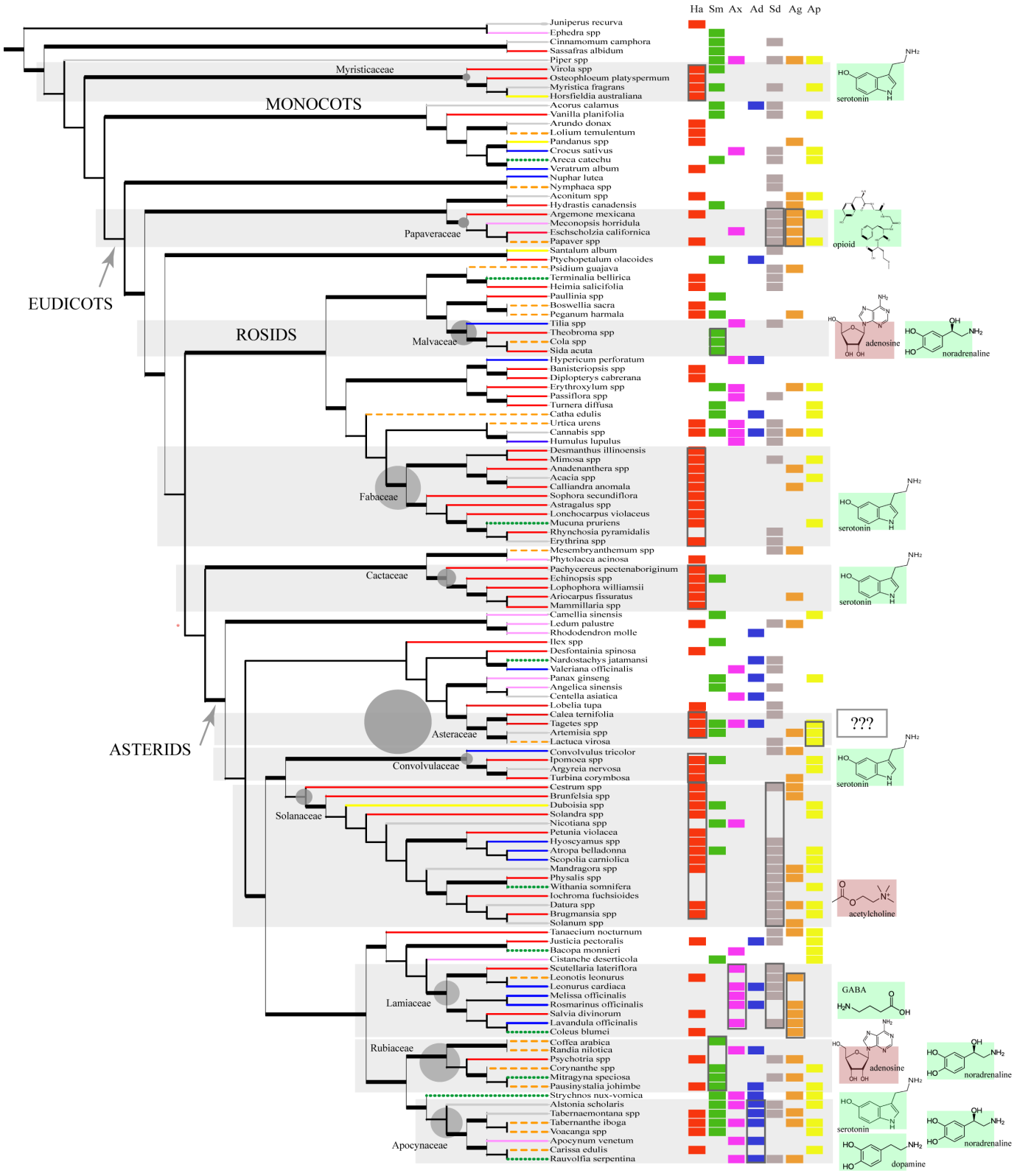
755 **Figure 1. The phylogeny (cladogram) of traditionally used psychoactive plant taxa.** The
756 phylogeny conforms to expected groupings (APG IV, 2016). The 11 main plant families are
757 highlighted (top to bottom): Myristicaceae, Papaveraceae, Malvaceae, Fabaceae, Cactaceae,
758 Asteraceae, Convolvulaceae, Solanaceae, Lamiaceae, Rubiaceae, Apocynaceae. Grey circles
759 next to their family names are proportional to total generic diversity within the family with
760 lowest count for Myristicaceae (21genera), and highest with 1623 genera for Asteraceae
761 (Christenhusz and Byng 2016). Branches are coded according to the different cultures (Native
762 American: red solid line; Middle Eastern and African: orange dashed line; European: blue solid
763 line; Indomalayan: green dotted line; Temperate Asia: pink solid line, Australasia: yellow solid
764 line; Multi-cultural: grey solid line). Branches in bold represent bootstrap node support >50%
765 and SH-like branch support >0.9. Psychoactive uses were overlain next to taxon names in
766 columns (Ha=hallucinogen, Sm=stimulant, Ax=anxiolytic, Ad=antidepressant, Sd=sedative,
767 Ag=analgesic, Ap=aphrodisiac along with the primary neurotransmitters affected by the
768 phytochemical/s exerting the dominant psychoactive effect (delineated with boxes; cf. Table 2).
769 Shaded plant families with phytochemicals that activate certain neurotransmitter systems (e.g.
770 receptor agonists) show the neurotransmitter/s involved with green (bright) background;
771 phytochemicals with inhibitory effects to the NT have red (dark) background. In Asteraceae,
772 neuropharmacology is unclear (???).


Ha Sm Ax Ad Sd Ag Ap
Juniperus recurva
Ephedra spp
Cinnamomum camphora
Sassafras albidum
Piper spp
Virola spp
Osteophloeum platyspermum
Myristica fragrans
Horsfieldia australiana
Myristicaceae
MONOCOTS
Acorus calamus
Vanilla planifolia
Arundo donax
Lolium temulentum
Pandanus spp
Crocus sativus
Areca catechu
Veratrum album
Nuphar lutea
Nymphaea spp
Aconitum spp
Hydrastis canadensis
Argemone mexicana
Meconopsis horridula
Eschscholzia californica
Papaver spp
Papaveraceae
EUDICOTS
Santalum album
Ptychopetalum olacoides
Psidium guajava
Terminalia bellirica
Heimia salicifolia
Paullinia spp
Boswellia sacra
Peganum harmala
ROSIDS
Tilia spp
Theobroma spp
Cola spp
Sida acuta
Malvaceae
Hypericum perforatum
Banisteriopsis spp
Diplopterys cabrerana
Erythroxylum spp
Passiflora spp
Turnera diffusa
Catha edulis
Urtica urens
Cannabis spp
Humulus lupulus
Desmanthus illinoensis
Mimosa spp
Anadenanthera spp
Acacia spp
Calliandra anomala
Fabaceae
Sophora secundiflora
Astragalus spp
Lonchocarpus violaceus
Mucuna pruriens
Rhynchosia pyramidalis
Erythrina spp
Mesembryanthemum spp
Phytolacca acinosa
Pachycereus pectenaboriginum
Cactaceae
Echinopsis spp
Lophophora williamsii
Ariocarpus fissuratus
Mammillaria spp
Camellia sinensis
Ledum palustre
Rhododendron molle
Ilex spp
Desfontainia spinosa
Nardostachys jatamansi
Valeriana officinalis
Panax ginseng
Angelica sinensis
Centella asiatica
Lobelia tupa
Calea ternifolia
Tagetes spp
Artemisia spp
Asteraceae
Lactuca virosa
ASTERIDS
Convolvulus tricolor
Ipomoea spp
Argyreia nervosa
Turbina corymbosa
Convolvulaceae
Cestrum spp
Brunfelsia spp
Duboisia spp
Solandra spp
Solanaceae
Nicotiana spp
Petunia violacea
Hyoscyamus spp
Atropa belladonna
Scopolia carniolica
Mandragora spp
Physalis spp
Withania somnifera
Iochroma fuchsioides
Datura spp
Brugmansia spp
Solanum spp
Tanaecium nocturnum
Justicia pectoralis
Bacopa monnieri
Cistanche deserticola
Scutellaria lateriflora
Leonotis leonurus
Leonurus cardiaca
Melissa officinalis
Rosmarinus officinalis
Lamiaceae
Salvia divinorum
Lavandula officinalis
Coleus blumei
Coffea arabica
Rubiaceae
Randia nilotica
Psychotria spp
Corynanthe spp
Mitragyna speciosa
Pausinystalia johimbe
Strychnos nux-vomica
Alstonia scholaris
Tabernaemontana spp
Tabernanthe iboga
Voacanga spp
Apocynaceae
Apocynum venetum
Carissa edulis
Rauvolfia serpentina
serotonin
opioid
adenosine
noradrenaline
???
acetylcholine
GABA
dopamine

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775 **Figure 2. Cultural distribution of psychoactive applications.** Psychoactive plants were
776 categorized according to cultural affiliation and psychoactive uses. Each row shows the
777 distribution of psychoactive uses for plants within a cultural group. Of the 126 psychoactive
778 plant genera, more than half of the plants are used as hallucinogens mostly by Native Americans.
779 Plants with sedative/narcotic qualities are also commonly sought after. Plants with anxiolytic and
780 antidepressant effects are the least popular among different cultures.

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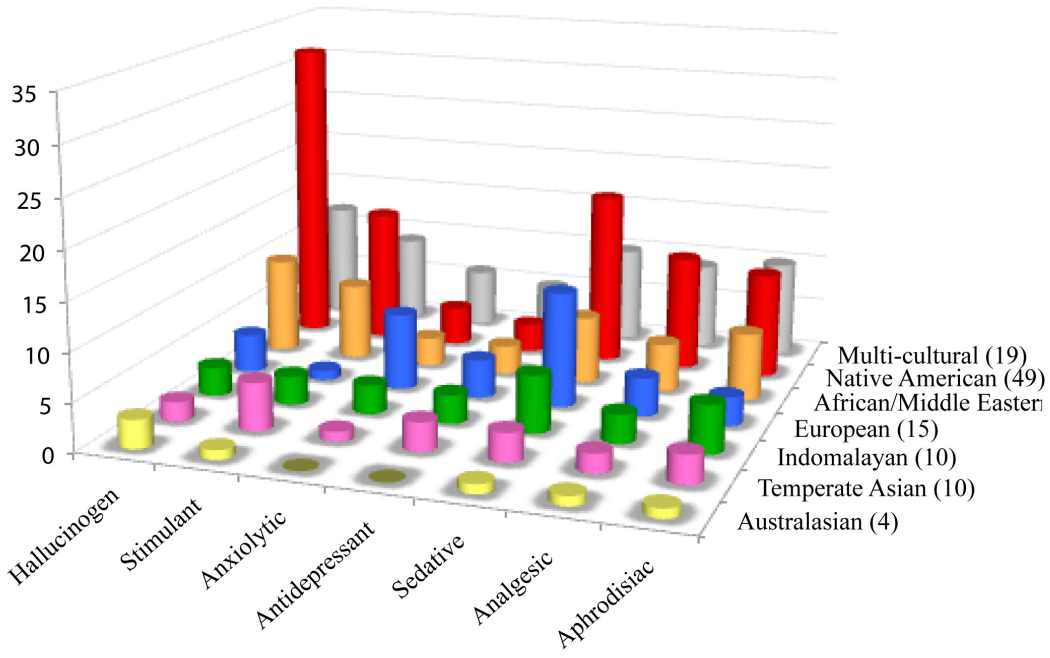

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Table 1. Psychoactive plant taxa in this study. Culturally diverse psychoactive plant taxa, their uses, indigenous psychoactive cultural origin, and corresponding Genbank numbers.

Family (Order)	Accepted binomial name	Common Name	Indigenous psychoactive culture	Mechanism of Action	Genbank Numbers
Acanthaceae (Lamiales)	*Justicia pectoralis* Jacq.	justicia	Native American (Rätsch, 2005)	Hallucinogen, antidepressant, sedative, aphrodisiac (Rätsch, 2005)	AJ879453
Acoraceae (Acorales)	*Acorus calamus* L.	sweet flag	Indomalayan, Temperate Asian (Rätsch, 2005)	Stimulant, antidepressant, sedative (Rätsch, 2005)	AJ879453
Aizoaceae (Caryophyllales)	*Mesembryan-themum* spp.	ice plant	African and Middle Eastern (Rätsch, 2005)	Sedative, analgesic (Rätsch, 2005)	HM850175
Apiaceae (Apiales)	*Angelica sinensis (*Oliv.) Diels	dong quai	Temperate Asian (Rätsch, 2005)	Stimulant, sedative (O'Mahony, 2010)	GQ436632

Apiaceae (Apiales)	*Centella asiatica* (L) Urb.	gotu kola	Indomalayan, Temperate Asian (Rätsch, 2005)	Antianxiety, antidepressant (Mamedov, 2005)	GQ436635
Apocynaceae (Gentianales)	*Alstonia scholaris* (L.) R. Br.	dita	African and Middle Eastern, Australasian, Indomalayan (Rätsch, 2005; Arulmozhi et al., 2012)	Stimulant, antianxiety, antidepressant, sedative, analgesic, aphrodisiac (Rätsch, 2005; Arulmozhi et al., 2012)	EU916739
Apocynaceae (Gentianales)	*Apocynum venetum* L	luobuma	Temperate Asian (Grundmann et al. 2007)	Antianxiety, antidepressant (Grundmann et al. 2007; Zheng, Fan & Liu, 2013)	KP088474
Apocynaceae (Gentianales)	*Carissa edulis* (Forssk.) Vahl	Arabian numnum	African and Middle Eastern (Rätsch, 2005)	Hallucinogen, aphrodisiac (Rätsch, 2005)	JF265327

Apocynaceae (Gentianales)	*Rauvolfia serpentina* (L.) Benth. ex Kurz	snakeroot	Indomalayan (Mamedov, 2005)	Antianxiety, antidepressant, sedative, analgesic (Spinella 2001; Mamedov, 2005; Rätsch, 2005)	KJ667614
Apocynaceae (Gentianales)	*Tabernaemontana* spp.	milkweed	Indomalayan, African, Native American (Rätsch, 2005)	Hallucinogen, stimulant, antidepressant, sedative, analgesic (Rätsch, 2005; Pratchayasakul et al., 2008; Cardoso et al. 2015)	EU916740
Apocynaceae (Gentianales)	*Tabernanthe iboga* Baill.	iboga	African and Middle Eastern (Sayin, 2014)	Hallucinogen, stimulant, antianxiety, antidepressant, analgesic, aphrodisiac (Nigg and Seigler, 2013; Sayin, 2014)	AJ419763
Apocynaceae (Gentianales)	*Voacanga* spp.	voacango bush	African and Middle Eastern	Hallucinogen, stimulant, aphrodisiac (Rätsch, 2005)	KC628529

			(Rätsch, 2005)		
Aquifoliaceae (Aquifoliales)	*Ilex* spp.	yerba mate	Native American (Rätsch, 2005)	Stimulant (Rätsch, 2005)	FJ394625
Araliaceae (Apiales)	*Panax ginseng* C.A.Mey.	ginseng	Temperate Asian (Rätsch, 2005)	Stimulant, antidepressant, aphrodisiac (Rätsch, 2005)	KM088019
Arecaceae (Arecales)	*Areca catechu* L.	betel nut	Indomalayan (Rätsch, 2005)	Stimulant, sedative, aphrodisiac (Rätsch, 2005)	JX571781
Asteraceae (Asterales)	*Artemisia* spp.	wormwood	European; Temperate Asian (Rätsch, 2005; Sayin, 2014)	Hallucinogen, stimulant, analgesic aphrodisiac (Rätsch, 2005; Sayin, 2014)	KM360653
Asteraceae (Asterales)	*Calea ternifolia* Oliv	dream herb	Native American (Rätsch, 2005)	Hallucinogen, sedative (Rätsch, 2005)	AY215089
Asteraceae (Asterales)	*Lactuca virosa* Habl.	wild lettuce	African and Middle Eastern (Rätsch, 2005)	Sedative, aphrodisiac (Rätsch, 2005)	KM360888

Asteraceae (Asterales)	*Tagetes* spp.	Mexican marigold	Native American (Rätsch, 2005)	Hallucinogen, stimulant, antianxiety, antidepressant, , aphrodisiac (Rätsch, 2005)	AY215184
Bignoniaceae (Lamiales)	*Bignonia nocturna* (Barb.Rodr.) L.G.Lohmann [=*Tanaecium nocturnum* (Barb.Rodr.) Burea & K.Schum.]	koribo	Native American (Rätsch, 2005).	Sedative, analgesic and aphrodisiac (Rätsch, 2005).	KR534325
Burseraceae (Sapindales)	*Boswellia sacra* Flueck.	olibanum tree	African and Middle Eastern (Rätsch, 2005)	Hallucinogen (Rätsch, 2005)	KT934315
Cactaceae (Caryophyllales)	*Ariocarpus fissuratus*	chautle	Native American (Rätsch, 2005)	Hallucinoge, analgesic ((Rätsch, 2005; Voogelbreinder 2009)	KC777009

	(Engelm.) K.Schum.				
Cactaceae (Caryophyllales)	*Echinopsis* spp. (incl. *Trichocereus pachanoi* Britton & Rose)	San Pedro cactus	Native American (Rätsch, 2005)	Hallucinogen, stimulant (Rätsch, 2005)	FR853367
Cactaceae (Caryophyllales)	*Lophophora williamsii* (Lem. Ex Salm-Dyck) J.M. Coult.	peyote	Native American (Vetulani, 2001)	Hallucinogen (Vetulani, 2001)	KC777011
Cactaceae (Caryophyllales)	*Mammillaria* spp.	false peyote	Native America (Rätsch, 2005)	Hallucinogen (Rätsch, 2005)	KC777008
Cactaceae (Caryophyllales)	*Pachycereus pecten-aboriginum* (Engelm. ex S. Watson) Britton &	pitayo	Native American (Schultes, 1976)	Hallucinogen (Schultes, 1976)	JN191499

	Rose				
Campanulaceae (Asterales)	*Lobelia tupa* L.	tupa	Native American (Schultes, 1976)	Hallucinogen, sedative (Schultes, 1976; Rätsch, 2005)	EF174606
Cannabaceae (Rosales)	*Cannabis* spp.	marijuana	Indomalayan, Temperate Asian (Rätsch, 2005)	Hallucinogen, stimulant, antianxiety, antidepressant, sedative, analgesic, aphrodisiac (Rätsch, 2005)	AF500344
Cannabaceae (Rosales)	*Humulus lupulus* L.	hops	European (Rätsch, 2005)	Antianxiety, sedative (Heinrich et al. 2012; McCall et al., 2013)	KT266264
Caprifoliaceae (Dipsacales)	*Nardostachys jatamansi* (D. Don) DC.	jatamansi	Indomalaya (Chaudhary et al. 2015)	Antidepressant, sedative (Chaudhary et al. 2015)	AF446950
Caprifoliaceae (Dipsacales)	*Valeriana officinalis* L.	valerian	European (Heinrich et al., 2012)	Antianxiety and sedative (Heinrich et al., 2012)	AY362490

Celastraceae (Calastrales)	*Catha edulis* (Vahl) Endl.	khat	African and Middle Eastern (Rätsch, 2005)	Stimulant, antidepressant, aphrodisiac (Rätsch, 2005)	JQ412336
Columelliaceae (Bruniales)	*Desfontainia spinosa* Ruiz & Pav.	taique	Native American (Rätsch, 2005)	Hallucinogen (Rätsch, 2005)	Z29670
Combretaceae (Myrtales)	*Terminalia bellirica* (Gaertn.) Roxb.	bellerian myrobalan	Indomalaya (Rätsch, 2005).	Hallucinogen, sedative (Rätsch, 2005).	KT279740
Convolvulaceae (Solanales)	*Argyreia nervosa* (Burm. F.) Bojer (=*Argyreia speciosa* (L. f.) Sweet)	Hawaiian baby	Native American (Rätsch, 2005)	Hallucinogen, analgesic, aphrodisiac (Rätsch, 2005; Galani, Patel & Patel 2010)	KF242477
Convolvulaceae (Solanales)	*Convolvulus tricolor* L.	dwart morning glory	European (Rätsch, 2005)	Sedative, analgesic (Rätsch, 2005)	L11683

Convolvulaceae (Solanales)	*Ipomoea* spp.	morning glory	Native American (Rätsch, 2005)	Hallucinogen, stimulant, aphrodisiac (Rätsch, 2005; Meira et al. 2012)	KF242478
Convolvulaceae (Solanales)	*Turbina corymbosa* (L.) Raf.	ololiuqui vine	Native American (Rätsch, 2005).	Hallucinogen, analgesic (Rätsch, 2005).	AY100966
Cupressaceae (Pinales)	*Juniperus recurva* Buch.-Ham. ex D. Don	Himalayan weeping juniper	Indomalayan, Temperate Asian (Rätsch, 2005)	Hallucinogen (Rätsch, 2005)	JQ512552
Ephedraceae (Ephedrales)	*Ephedra* spp.	ephedra	Temperate Asian (Heinrich et al., 2012)	Stimulant (Rätsch, 2005)	AY056562
Ericaceae (Ericales)	*Ledum palustre* L.	wild rosemary	Temperate Asian (Rätsch, 2005)	Hallucinogen, sedative, analgesic (Rätsch, 2005)	AF419831
Ericaceae (Ericales)	*Rhododendron molle* G.Don.	yang zhi zhu	Temperate Asian (Mamedov, 2005)	Antidepressant (Mamedov, 2005)	AF421101

Erythroxylaceae (Malpighiales)	*Erythroxylum* spp.	Coca	Native American (Rätsch, 2005).	Stimulant, antianxiety, analgesic and aphrodisiac (Rätsch, 2005)	AB925614
Fabaceae (Fabales)	*Acacia* spp.	wattle	African/Middle Eastern Australasian, Indomalayan, Native American, (Rätsch, 2005)	Hallucinogen, aphrodisiac (Rätsch, 2005)	HM849736
Fabaceae (Fabales)	*Anadenanthera* spp.	vilca, yopo	Native American (Rätsch, 2005)	Hallucinogen and analgesic (Schultes, 1976)	KJ082119
Fabaceae (Fabales)	*Astragalus* spp.	milk vetch	Native America (Rätsch, 2005)	Hallucinogen (Rätsch, 2005)	KU666554
Fabaceae (Fabales)	*Calliandra anomala* (Kunth) J.F. Macbr.	cabellito	Native American (Rätsch, 2005)	Hallucinogen and analgesic (Rätsch, 2005)	AM234255

Fabaceae (Fabales)	*Desmanthus illinoensis* (Michx.) MacMill.	prairie bundle flower	Native American (Halpern, 2004)	Hallucinogen (Halpern, 2004)	KP126868
Fabaceae (Fabales)	*Erythrina* spp.	coral trees	Native American, Indomalaya (Rätsch, 2005).	Hallucinogen and sedative (Rätsch, 2005).	AB045801
Fabaceae (Fabales)	*Lonchocarpus violaceus* Benth.	balche' tree	Native American (Rätsch, 2005)	Hallucinogen (Rätsch, 2005)	JQ626245
Fabaceae (Fabales)	*Mimosa* spp.	mimosa	Native American, Indomalayan (Rätsch, 2005)	Hallucinogenic, sedative, aphrodisiac (Rätsch, 2005)	KJ773686
Fabaceae (Fabales)	*Mucuna pruriens* (L.) DC.	velvet bean	Indomalayan (Lampariello, Cortelazzo & Guerranti, 2012)	Hallucinogen, aphrodisiac (O'Mahony, 2010; (Lampariello, Cortelazzo & Guerranti, 2012)	EU128734
Fabaceae	*Rhynchosia*	bird's eyes	Native American	Sedative (Rätsch, 2005)	KJ594450

(Fabales)	*pyramidalis* (Lam.) Urb.		(Rätsch, 2005)		
Fabaceae (Fabales)	*Sophora secundiflora* (Ortega) DC.	mescal bean	Native American (Schultes, 1976)	Hallucinogen (Schultes, 1976)	Z70141
Hypericaceae (Malpighiales)	*Hypericum perforatum* L.	St. John's wort	European (Spinella 2001)	Antianxiety, antidepressant (Spinella 2001; Heinrich et al., 2012)	AF206779
Iridaceae (Asparagales)	*Crocus sativus* L.	saffron	European (Rätsch, 2005)	Antianxiety, sedative, aphrodisiac (Rätsch, 2005; Hosseinzadeh,& Noraei 2009)	KF886671
Lamiaceae (Lamiales)	*Lavandula angustifolia* Mill. (=*Lavandula officinalis* Chaix)	lavender	European (Rätsch, 2005)	Antianxiety, sedative, analgesic (Lis-Balchin & Hart, 1999; Hajhashemi, Ghannadi & Sharif, 2003)	KT948988
Lamiaceae	*Leonotis leonurus*	lion's tail	African and	Hallucinogen, sedative, analgesic	AM234998

(Lamiales)	(L.) R. Br.		Middle Eastern (Rätsch, 2005)	(Rätsch, 2005)	
Lamiaceae (Lamiales)	*Leonurus cardiaca* L.	motherwort	European (Rauwald et al., 2015)	Antianxiety, antidepressant, sedative (Rauwald et al., 2015)	KM360848
Lamiaceae (Lamiales)	*Melissa officinalis* L.	lemon balm	European (Vogl et al., 2013)	Antianxiety, sedative (Heinrich et al. 2012)	KM360879
Lamiaceae (Lamiales)	*Plectranthus scutellarioides* (L.) R.Br. (=*Coleus blumei* Benth.)	coleus	Indomalayan (Rätsch, 2005)	Hallucinogen, analgesic (Rätsch, 2005)	JQ933273
Lamiaceae (Lamiales)	*Rosmarinus officinalis* L.	rosemary	European (Ferlemi et al. 2015)	Antianxiety, antidepressant, analgesic (Ferlemi et al. 2015	KR232566
Lamiaceae (Lamiales)	*Salvia divinorum* Epling & Jativa	yerba de la pastora	Native American (Rätsch, 2005)	Hallucinogen, analgesic (Rätsch, 2005)	AY570410

Lamiaceae (Lamiales)	*Scutellaria lateriflora* L.	skullcap	Native American (Awad et al., 2003)	Antianxiety, sedative (Awad et al., 2003)	HQ590266
Lauraceae (Laurales)	*Cinnamomum camphora (L.)* J. Presl	camphor	Indomalayan, Temperate Asian (Rätsch, 2005)	Stimulant, sedative, (Rätsch, 2005)	L12641
Lauraceae (Laurales)	*Sassafras albidum* (Nutt.) Nees	sassafras	Native American (Rätsch, 2005)	Stimulant (Rätsch, 2005)	AF206819
Loganiaceae (Gentianales)	*Strychnos nux-vomica* L.	strychnine tree	Indomalaya (Rätsch, 2005)	Stimulant, antianxiety, antidepressant, aphrodisiac (Rätsch, 2005)	L14410
Lythraceae (Myrtales)	*Heimia salicifolia* (Kunth) Link	sinicuiche	Native American (Rätsch, 2005)	Hallucinogen, sedative (Rätsch, 2005)	AY905410
Malpighiaceae (Malpighiales)	*Banisteriopsis* spp.	ayahuasca	Native American (Sayin, 2014)	Hallucinogen (Sayin, 2014)	HQ247440
Malpighiaceae	*Diplopterys*	chaliponga	Native American	Hallucinogen (O'Mahony, 2010).	HQ247482

(Malpighiales)	*cabrerana* (Cuatrec) B. Gates		(Sayin, 2014)		
Malvaceae (Malvales)	*Cola* spp.	kola nut	Africa and Middle Eastern (McClatchey et al., 2009)	Stimulant (McClatchey et al., 2009)	AY082353
Malvaceae (Malvales)	*Sida acuta* Burm.f.	broomweed	Native America (Rätsch, 2005)	Stimulant (Rätsch, 2005)	KJ773888
Malvaceae (Malvales)	*Theobroma* spp.	cacao	Native American (Rätsch, 2005).	Stimulant (Rätsch, 2005).	JQ228389
Malvaceae (Malvales)	*Tilia* spp.	linden	European (Rätsch, 2005)	Antianxiety, sedative (Rätsch, 2005)	KT894775
Melanthiaceae (Liliales)	*Veratrum album* L.	white hellebore	European (Rätsch, 2005)	Hallucinogen (Rätsch, 2005)	KM242984
Myristicaceae (Magnoliales)	*Horsfieldia australiana* S. T.	nutmeg	Australasian, (Rätsch, 2005)	Hallucinogen (Rätsch, 2005)	KF496315

	Blake				
Myristicaceae (Magnoliales)	*Myristica fragrans* Houtt.	nutmeg	Australiasia, Indomalaya (Rätsch, 2005)	Hallucinogen, stimulant, sedative aprhodisiac (Rätsch, 2005)	AF206798
Myristicaceae (Magnoliales)	*Osteophloeum platyspermum* (Spruce ex A.DC.) Warb.	huapa	Native American (Rätsch, 2005)	Hallucinogen (Rätsch, 2005)	JQ625884
Myristicaceae (Magnoliales)	*Virola elongata* (Benth.) Warb.	epena	Native American (Rätsch, 2005)	Hallucinogen, stimulant (Rätsch, 2005)	JQ626043
Myrtaceae (Myrtales)	*Psidium guajava* L.	guava	African and Middl eastern (Rätsch, 2005)	Sedative, analgesic (Rätsch, 2005)	JQ025077
Nitrariaceae (Sapindales)	*Peganum harmala* L.	harmal	African and Middle Eastern (Sayin, 2014)	Hallucinogen, stimulant, analgesic (Vetulani, 2001; Farouk et al., 2008)	DQ267164

Nymphaeaceae (Nymphaeales)	*Nuphar lutea* (L.) Sm.	yellow water lily	European (Rätsch, 2005)	Sedative (Rätsch, 2005)	DQ182338
Nymphaeaceae (Nymphaeales)	*Nymphaea* spp.	water lily	African and Middle eastern (Rätsch, 2005)	Sedative (Rätsch, 2005)	GQ468660
Olacaceae (Santalales)	*Ptychopetalum olacoides* Benth.	marapuama	Native American (Piato et al., 2008)	Stimulant, Antidepressant (Piato et al., 2008)	FJ038139
Orchidaceae (Asparagales)	*Vanilla planifolia* Jacks. ex Andrews	vanilla	Native America (Rätsch, 2005)	Stimulant, sedative, aphrodisiac (Rätsch, 2005; O'Mahony, 2010)	KJ566306
Orobanchaceae (Lamiales)	*Cistanche deserticola* K.C.Ma	rou cong rong	Temperate Asian (Wang, Zhang & Xie, 2012)	Stimulant, aphrodisiac (O'Mahony, 2010)	KC128846
Pandanaceae (Pandanales)	*Pandanus* spp.	screwpine	Australasian (Rätsch, 2005)	Hallucinoge, analgesic ((Rätsch, 2005)	JX903247

Papaveraceae (Ranunculales)	*Argemone mexicana* L.	Mexican poppy	Native American (Rätsch, 2005)	Hallucinogen, sedative, analgesic, aphrodisiac (Rätsch, 2005; Brahmachari, Gorai & Roy, 2013)	U86621
Papaveraceae (Ranunculales)	*Eschscholzia californica* Cham.	California poppy	Native American (Rolland et al., 1991)	Antianxiety, sedative, analgesic (Rolland et al., 1991)	KM360775
Papaveraceae (Ranunculales)	*Meconopsis horridula* Hook. f. & Thomson	prickly blue poppy	Temperate Asian (Fan et al., 2015)	Sedative, analgesic (Fan et al., 2015)	JX087717
Papaveraceae (Ranunculales)	*Papaver somniferum* L.	opium poppy	African and Middle Eastern (Vetulani, 2001)	Hallucinogen, sedative, analgesic, aphrodisiac (Rätsch, 2005)	KU204905
Passifloraceae (Malpighiales)	*Passiflora* spp.	passion flower	Native American (Rätsch, 2005)	Antianxiety, sedative (Heinrich et al. 2012)	HQ900864
Passifloraceae (Malpighiales)	*Turnera diffusa* Willd. ex Schult.	damiana	Native American (Rätsch, 2005)	Stimulant, antianxiety, aphrodisiac (Rätsch, 2005)	JQ593109

Phytolaccaceae (Caryophyllales)	*Phytolacca acinosa* Roxb.	pokeweed	Temperate Asian (Rätsch, 2005)	Hallucinogen (Rätsch, 2005)	HM850257
Piperaceae (Piperales)	*Arundo donax* L.	giant reed	African and Middle Eastern; Native American (Rätsch, 2005)	Hallucinogen (Rätsch, 2005)	U13226
Piperaceae (Piperales)	*Piper* spp.	pepper, kava	Native American, Indomalayan, Australasian (Rätsch, 2005)	Stimulant, antianxiety, sedative, analgesic, aphrodisiac (Rätsch, 2005)	AY032642
Plantaginaceae (Lamiales)	*Bacopa monnieri* (L.) Wettst.	brahmi	Indomalayan (Shinomol, Muralidhara, Bharath 2011)	Antianxiety, aphrodisiac (Shinomol, Muralidhara, Bharath 2011)	KJ773301
Poaceae (Poales)	*Lolium temulentum* L.	bearded darnel	African and Middle Eastern	Hallucinogen (Rätsch, 2005)	KM538829

			(Rätsch, 2005)		
Ranunculaceae (Ranunculales)	*Aconitum* spp.	monkshood	European, Indomalayan, Temperate Asian (Rätsch, 2005)	Hallucinogen, analgesic, aphrodisiac (Rätsch, 2005)	EU053898
Ranunculaceae (Ranunculales)	*Hydrastis canadensis* L.	goldenseal	Native American (Foster and Duke, 2000)	Stimulant, sedative, analgesic (O'Mahony, 2010)	L75849
Rubiaceae (Gentianales)	*Catunaregam nilotica* (Stapf) Tirveng. (=*Randia nilotica* Stapf)	chibra	Africa and Middle eastern (Danjuma et al. 2014)	Antianxiety, antidepressant (Danjuma et al. 2014)	AJ286700
Rubiaceae (Gentianales)	*Coffea arabica* L.	coffee	African and Middle Eastern (Rätsch, 2005)	Stimulant (Rätsch, 2005)	EF044213

Rubiaceae (Gentianales)	*Corynanthe* spp.	pamprama	African and Middle Eastern (Rätsch, 2005)	Stimulant and aphrodisiac (Rätsch, 2005)	AJ346977
Rubiaceae (Gentianales)	*Mitragyna speciosa* (Korth.) Havil	kratom	Indomalaya (Idayu et al, 2011; Suhaimi et al. 2016)	Stimulant, analgesic, sedative, (Rätsch, 2005; Suhaimi et al. 2016)	AJ346988
Rubiaceae (Gentianales)	*Pausinystalia johimbe* (K.Schum.) Pierre ex Beille	yohimbe	African and Middle Eastern (Rätsch, 2005)	Hallucinogen, stimulant, antidepressant, aphrodisiac (Rätsch, 2005)	AJ346998
Rubiaceae (Gentianales)	*Psychotria* spp.	chacruna	Native American (Rätsch, 2005)	Hallucinogen, sedative, analgesic (Rätsch, 2005)	KJ805654
Santalaceae (Santalales)	*Santalum murrayanum* C.A Gardner	sandalwood	Australasian (Rätsch, 2005)	Sedative (Rätsch, 2005)	L26077

Sapindaceae (Sapindales)	*Paullinia* spp.	guarana	Native American (McClatchey et al., 2009)	Stimulant (McClatchey et al., 2009)	AY724365
Solanaceae (Solanales)	*Atropa belladonn*a L.	belladonna	European (Schultes, 1976)	Hallucinogen, stimulant, sedative, aphrodisiac (Rätsch, 2005)	AJ316582
Solanaceae (Solanales)	*Brugmansia* spp.	angel's trumpet	Native American (Rätsch, 2005)	Hallucinogen, sedative, aphrodisiac (Rätsch, 2005)	HM849829
Solanaceae (Solanales)	*Brunfelsia* spp.	raintree	Native American (Rätsch, 2005)	Hallucinogen, analgesic (Rätsch, 2005)	AY206720
Solanaceae (Solanales)	*Cestrum* spp.	flowering jessamine	Native American (Rätsch, 2005)	Hallucinogen, sedative, analgesic (Rätsch, 2005)	JX572398
Solanaceae (Solanales)	*Datura* spp.	toloache	Native American, Indomalayan, European (Rätsch, 2005)	Hallucinogen, sedative, analgesic, aphrodisiac (Rätsch, 2005)	JX996059

Solanaceae (Solanales)	*Duboisia* spp.	pituri	Australasian (Rätsch, 2005)	Hallucinogen, stimulant, aphrodisiac (Rätsch, 2005)	KM895868
Solanaceae (Solanales)	*Hyoscyamus* spp.	Henbane	European (Rätsch, 2005)	Hallucinogen. sedative (Rätsch, 2005)	KF248009
Solanaceae (Solanales)	*Iochroma fuchsioides* (Bonpl.) Miers	yas	Native American (Rätsch, 2005)	Sedative (Rätsch, 2005)	KU310432
Solanaceae (Solanales)	*Mandragora* spp.	mandrake	European, African and Middle Eastern (Rätsch, 2005; Sayin, 2014)	Hallucinogen, sedative, analgesic, aphrodisiac (Rätsch, 2005; Sayin, 2014)	U08614
Solanaceae (Solanales)	*Nicotiana* spp.	tobacco	Native American, Australasian (Vetulani, 2001;	Stimulant, antianxiety (Rätsch, 2005)	KU199713

			Rätsch, 2005)		
Solanaceae (Solanales)	*Petunia violacea* Lindl.	shanin	Native American (Schultes, 1976)	Hallucinogen (Schultes, 1976)	HQ384915
Solanaceae (Solanales)	*Physalis* spp.	groundcherry	Native American (Rätsch, 2005)	Sedative, analgesic (Rätsch, 2005)	KP295964
Solanaceae (Solanales)	*Scopolia carniolica* Jacq.	scopolia	European (Rätsch, 2005)	Hallucinogen, sedative, aphrodisiac (Rätsch, 2005)	HQ216145
Solanaceae (Solanales)	*Solandra* spp.	arbol del viento	Native American (Knab 1977; Rätsch, 2005)	Hallucinogen, aphrodisiac (Knab 1977; Rätsch, 2005)	U08620
Solanaceae (Solanales)	*Solanum* spp.	nightshade	European, Native American, (Rätsch, 2005)	Sedative, analgesic (Rätsch, 2005)	KC535803
Solanaceae (Solanales)	*Withania somnifera* (L.)	ashwagandha	Indomalayan (Rätsch, 2005)	Sedative, aphrodisiac (Rätsch, 2005)	FJ914179

	Dunal				
Theaceae (Ericales)	*Camellia sinensis* (L.) Kuntze	tea	Temperate Asian (Rätsch, 2005)	Stimulant, aphrodisiac (Rätsch, 2005)	EU053898
Urticaceae (Rosales)	*Urtica urens* L.	nettle	African and Middle Eastern (Doukkali et al., 2015)	Hallucinogen, antianxiety, sedative (O'Mahony, 2010; Doukkali et al., 2015)	KM361027

Table 2. Main psychoactive families (cf. Fig. 1), their primary psychoactive effect, suspected phytochemical constituents producing the effect, and the primary neurotransmitter (NT) systems potentially affected. "+/-" refers to the activation (receptor agonist) and inhibition (receptor antagonist), respectively, of certain NT receptors by the psychoactive substance.

Family	Main psychoactive effect	Active phytochemicals	Neurotransmitter systems affected
Apocynaceae	Antidepressant	Indole alkaloids, e.g. ibogaine, rauwolscine, reserpine, yohimbine (Spinella 2001; Polya, 2003; Rätsch, 2005; Pratchayasakul et al. 2008; Sayin, 2014; Cardoso et al. 2015)	Serotonin (+), dopamine (+), noradrenaline (+) (Wells, Lopez & Tanaka, 1999; Spinella, 2001; Polya, 2003; Grundmann et al. 2007; Arulmozhi et al., 2012; Zheng, Fan & Liu, 2013; Sayin, 2014; Cardoso et al. 2015) [except reserpine but other indole alkaloids may counteract its effects (Polya, 2003)]
Asteraceae	Hallucinogen, aphrodisiac	Sesquiterpene lactones (Rätsch, 2005; Sayin, 2014)	Unknown mechanisms for various sesquiterpene lactones (Chadwick et al. 2013)
Cactaceae	hallucinogen	Phenethylamine alkaloids, e.g.	Serotonin (+) (Polya, 2003)

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		hordenine, mescaline, pectenine (Rätsch, 2005; Sayin, 2014).	
Convolvulaceae	hallucinogen	Ergot indole alkaloids (Rätsch, 2005; McClatchey et al., 2009).	Serotonin (+) (Polya, 2003; Kennedy, 2014)
Fabaceae	Hallucinogen	Indole alkaloids, e.g. bufotenin, DMT; tryptamines (Polya, 2003; Halpern, 2004; Rätsch, 2005)	Serotonin (+)
Lamiaceae	Anxiolytic, sedative, analgesic	Terpenoids e.g. baicalin, linalool, labdane, rosmarinic acid, salvinorin A, wogonin, etc. (Lis-Balchin & Hart, 1999; Awad et al, 2003, 2009; Polya, 2003; Heinrich et al. 2012); leonurine alkaloid (Rauwald et al., 2015)	GABA (+) (Awad et al., 2003; 2009; Hajhashemi, Ghannadi & Sharif, 2003; Shi et al. 2014; Rauwald et al., 2015)
Malvaceae	Stimulant	Xanthine alkaloids, e.g. caffeine, theobromine (in *Cola,*	Adenosine (-) by xanthine alkaloids (Polya, 2003; McClatchey et al., 2009); adrenaline (+) by ephedrine

		Theobroma; Rätsch, 2005; McClatchey et al., 2009); phenethylamine ephedrine in *Sida;* Prakash, Varma, & Ghosal, 1981).	(Polya, 2003)
Myristicaceae	Hallucinogen	DMT (indole alkaloid in *Virola*); phenylpropene e.g. myristicin, elemicine, safrole (Polya, 2003; Rätsch, 2005)	Serotonin (+) (Spinella 2001; Polya, 2003)
Papaveraceae	Hallucinogen	Isoquinoline alkaloids, e.g. codeine; morphine; reticuline; thebaine (Polya, 2003; Heinrich et al. 2012; Fedurco et al. 2015; Shang et al., 2015)	Opioid (+) (Rolland et al, 1991; Polya, 2003; Shang et al., 2015)
Rubiaceae	Stimulant	caffeine (xanthine alkaloid in *Coffea*; Polya, 2003); indole	Adenosine (-) by xanthine alkaloids (Polya, 2003; McClatchey et al., 2009); adrenaline (+) and

		alkaloids in others, e.g. corynanthine, mitragynine, yohimbine (indole alkaloid; Polya, 2003; Rätsch, 2005; Suhaimi et al. 2016)	serotonin (+) by indole alkaloids (Polya, 2003)
Solanaceae	Hallucinogen, sedative,	Tropane alkaloids, e.g. atropine, hyoscyamine, scopolamine (Polya, 2003; Rätsch, 2005)	Acetycholine (-) (Polya, 2003)