Behavioural Brain Research 73 (1996) 109–115

Plant hallucinogens: springboards for psychotherapeutic drug discovery

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Abstract

Medicinal chemists have traditionally looked to the biosynthetic diversity found in nature to provide structural templates for the development of novel therapeutic agents, and the field of hallucinogen chemistry is similar to other fields in this respect. Even LSD, for many psychopharmacologists the prototype hallucinogen, is not itself a natural compound but rather is a semisynthetic analogue of alkaloids found in plants and fungi. A similar statement could be made about the other major structural classes of hallucinogenic agents: the phenylethylamine derivatives, the tryptamine derivatives, and the β-carboline derivatives. In each case, compounds occurring naturally in some plant, usually associated with a long tradition of ethnomedical or ceremonial use, have been the starting point for the synthesis of numerous analogues. Some of these, such as the methoxylated amphetamine derivatives, display a pharmacological profile that differs in important respects from their natural product templates. In some instances the analogues have proven to be useful tools in the hands of neurobiologists characterizing the structure and function of brain neurotransmitter systems; in other cases, they have led to the development of new psychopharmacological agents with realized or potential clinical utility. This paper gives a brief historical overview of the role of natural products in the history and development of medicinal chemistry and experimental pharmacology, particularly with respect to the development of psychopharmacology and the discovery of CNS-active agents. It discusses the potential for the discovery of new medications with psychotherapeutic and/or research applications though the investigation of plants and natural compounds with serotonergic activities. Finally, consideration is given to some lesser known plant hallucinogens which may provide further useful leads for psychotherapeutic drug discovery.

Keywords: Hallucinogen; Medicinal plant; Ethnomedicine; Natural product; Serotonin; Drug discovery; Psychopharmacology; Medicinal Chemistry

1. Introduction

The utilization of plants as therapeutic medicines is an ancient tradition, far older than the contemporary sciences of medicine, pharmacology, or chemistry; it is a tradition that can claim both historical and prehistoric precedent, having its origins in an era when medicine, magic, religion, and pharmacology were facets of a single empirical discipline. In many indigenous cultures, plant-based, traditional medicine has remained essentially unchanged from the form practiced by our ancestors 5000 or more years ago. Even in our contemporary era of sophisticated medicinal chemistry and pharmacological 'magic bullets', plant-derived medicines remain significant. The World Health Organization has estimated that over 75% of the world's population still relies on plant-derived medicines, usually obtained from traditional healers, for their basic health-care needs [1]. According to recent estimates, as many as 25% of currently available prescription drugs contain plant extracts or naturally occurring compounds, while at the same time, less than 10% of the earth's 400,000 to 750,000 plant species have been scientifically investigated for possible pharmacological activity [2]. Clearly the 90% of the world's flora that remains uninvestigated comprises a rich trove for the discovery of new therapeutic compounds, including those with neuropharmacological and psychopharmacological activity. The contributions to this discovery process that could be made through the systematic investigation of the chemistry and pharmacology of plant hallucinogens is the subject of the present paper.

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[1] Botanical Dimensions is a non-profit, 501(c)3 Organization dedicated to the investigation and preservation of plants of ethnomedical significance and their lore. Recently, Botanical Dimensions sponsored an interdisciplinary biomedical investigation of hoasca, a hallucinogenic beverage used throughout the Amazon Basin.

2. Natural products and the history of CNS drug development

Modern medicine, and the intimately associated disciplines of pharmacology and medicinal chemistry which provide physicians with the tools of their trade, have their historical roots in an earlier era in which the practice of medicine and the compounding of herbal remedies for specific illnesses were conducted as largely empirical activities, usually with no scientific basis and often, when a therapeutic rationale was provided at all, within a theoretical framework that resembled magic or superstition far more than contemporary models of disease or dysfunction [3]. Nevertheless, centuries of trial-and-error experimentation by shamans, herbalists, witches, alchemists, and other practitioners, inevitably lead to the discovery of the biodynamic properties of certain plants, and of these, it was plants affecting the nervous system and mental functions that often had the most profound and dramatic effects; the juice of certain poppies had the power to block pain and induce a dream-like sleep; chewing the leaves of other plants could induce a state of wakefulness and mental clarity; consumption of certain mushrooms or seeds could plunge the eater into a bizarre alternate reality, complete with visions, voices, and confrontations with gods (or demons). Given the unambiguous and occasionally terrifying effects of psychoactive plants, whether consumed accidentally or deliberately, it is little wonder that our ancestors early on developed a healthy respect for the power of plants to heal, as well as to derange and even to destroy.

Clever practitioners adapted the use of psychoactive and other biodynamic plants to their own purposes, incorporating them into quasi-medical practices as well as ceremonial and magical activities; gradually, people became more sophisticated in the herbal arts, sharing and transmitting the secrets of plant-lore between cultures and generations. New methods of preparing sophisticated, multicomponent 'recipes' were discovered, as were new technologies for extracting the 'essences' or 'spirit' of the plants. The discovery of steam distillation in the Middle Ages [4] was one such turning point, as it marked the appearance of one of the first pharmaceutical technologies that went beyond the preparation of simple aqueous decoctions (as well as enabling and fostering the development of perfumery).

It was not until the nineteenth century, however, that this natural desire to literally isolate the 'spirit' of plants in an ever more purified, concentrated, and potent form, stimulated the discoveries that eventually would form the foundations of modern organic chemistry, pharmacology, and pharmacotherapeutic medicine. And once again, psychoactive plants assumed center stage as the focus of the new phytochemical technologies. Morphine, from the opium poppy, isolated by the German pharmacist Sërtuner in 1803 [5], was the first alkaloid to be purified from a plant; this event marked the first scientific application of phytochemical technology that would lead to the isolation of the presumed 'active principles' from many of the important medicinal plants of the era, including cocaine from coca leaves (Squibb 1885) [6], and mescaline from the dried tops of the peyote cactus by Arthur Heffter in 1896 [7]. It was a fortunate accident of nature that these and other highly biodynamic plant constituents were alkaloids, and thus amenable to purification using relatively crude isolation methods.

3. Contributions of natural products to CNS drug development

Once isolated, the plant alkaloids contributed to the development and eventual ascendency of the view that physiological processes occurring in living organisms were fundamentally not different from physicochemical processes which could be studied and manipulated in a variety of systems, both living and non-living. Pharmacologists quickly found that the therapeutic actions of many important medicinal plants, could be replicated by the use of the purified 'active principle' alone; chemists discovered that these active principles were not magical 'essences', but in reality were complex organic compounds, with definite structures, molecular weights, melting points, and other physical properties. Moreover, chemists found that they could modify the structural characteristics of an isolated natural product using relatively simple methods, and that the pharmacological properties of the modified compound would often be altered as a result, sometimes in unexpected ways. These discoveries further eroded the notion that biodynamic plants were the dwelling place of some kind of 'healing spirit', or genii. Living things eventually came to be understood as systems (albeit extremely complex systems) which were governed by the laws of chemistry and physics alone, not by some mysterious and unmeasurable 'vital force' [8]; moreover, these systems were subject to manipulation, to pharmacologic intervention. Once these ideas gained general acceptance and became firmly entrenched in Western views of nature, only then were modern medicine, pharmaceutical technology, and medicinal chemistry able to come into their own.

The principles which were discovered in the 19th century through a combination of blind luck, trial and error, and deliberate experiment have today become enshrined as fundamental axioms of the process of drug discovery and development. Natural products, which provided the foundation of the field in the first place, continue to make their contributions felt in significant ways, and in much the same ways that they always have. Specifically, natural products, whether isolated from

plant, animal, or microbial sources, have provided and still provide medicinal chemists and pharmacologists with: (1) pharmacological research tools; (2) novel structural templates; and (3) leads to new pharmacologic mechanisms.

3.1. Research tools

Natural products provide pharmacologists with useful research tools for elucidating basic pharmacological mechanisms. Many examples could be cited here, but two that should be quite familiar to most neuroscientists are reserpine and forskolin. Reserpine, the major alkaloid of *Rauwolfia serpentina*, Indian Snake Root, has been used clinically as an antipsychotic tranquilizer and hypotensive medication [9]. While its clinical use has been all but supplanted by newer and more sophisticated medications, its ability to deplete neuronal vesicles of their stores of serotonin and catecholamines renders it a useful tool for pharmacologists studying processes related to neurotransmitter storage, synthesis, and release. Forskolin, a diterpene isolated from the medicinal mint, *Coleus forskolii*, provides another familiar example. Forskolin, in addition to having positive inotropic and antihypertensive properties in animal models, also is one of the most potent and specific activators of adenylate cyclase that has been discovered to date [10]. Hence, the compound has been used extensively by neuroscientists investigating the functions of adenylate cyclase, particularly the role of this enzyme in neurotransmitter systems coupled to adenylate cyclase-activated second messenger systems.

3.2. Novel structures

Natural products also provide medicinal chemists with ideas for novel structural templates; these are new molecular entities, whether synthetic or semi-synthetic, which bear a clear relationship to the natural product which provided the inspiration for their creation, but which may have unique pharmacological properties that are not shared by the parent compound; e.g., increased potency, reduced toxicity, antagonist as opposed to agonist action, or enhanced selectivity for a certain receptor population. The previous example, forskolin, can also be mentioned in this context; the related compound 1,9-deoxy forskolin, also isolated from the plant, has no stimulatory action on adenylate cyclase [11], while morpholine and piperidine derivatives of forskolin (7β-deactyl-7β[g-(morpholino) butyrl]-forskolin and 6β-[β'-(piperidino)propionyl]-forskolin, respectively) are water-soluble derivatives which equal or exceed the native compound in activating adenylate cyclase [12].

Further examples of the importance of natural products in the development of novel derivatives can be abundantly found by looking no further than morphine and cocaine, those hoary old 19th century alkaloids. A casual glance at Goodman and Gilman's Pharmacological Basis of Therapeutics [13] will reveal there numerous examples of cocaine and morphine analogs, all of which bear a clear structural resemblance or at least relationship to the natural alkaloids, but which may display a radically different pharmacological profile. The narcotic antagonist naloxone, which is close to morphine in structure but which is a potent opiate antagonist [14], and the compound CPT ((−)-2β-carbomethoxy-3β-phenyltropane), a cocaine analog which, like cocaine itself, binds with high affinity to the dopamine transporter and induces a response similar to cocaine in animal behavioral models, provide two examples [15]. In fact, it would not be an extreme exaggeration to assert that, in the case of cocaine and morphine, the creation and pharmacological characterization of analogs of these compounds has evolved into a small but significant subdiscipline of medicinal chemistry and neuropharmacology.

3.3. Novel mechanisms

The third area where natural products have significant impact on pharmacology lies in their usefulness in identifying new mechanisms of action, and/or novel or previously uncharacterized receptor populations mediating those mechanisms. Often, a structurally novel class of neuropharmacological agents can lead investigators to the discovery of a new class of receptors with which the compounds interact. The discovery of specific receptors for THC (tetrahydrocannabinol), the major psychoactive component of marijuana, provides one example; although THC has been known for years, identification of a receptor population selective for the drug was been accomplished only relatively recently; now that the receptors have been characterized and cloned, dozens of new ligands, some of which bear only the most superficial structural resemblance to THC, are now under investigation [16]. Some of these may eventually prove to have therapeutic properties similar to those that have been claimed for THC itself, such as hypotensive, antispasmodic, or antinauseant activity.

4. Serotonergic hallucinogens

The 'classical' hallucinogens, exemplified by compounds such as LSD, DMT, mescaline, or psilocybin, are all characterized by a serotonergic pharmacology; all display agonist activity at 5-HT_2 receptors, and there is evidence that some may interact with other 5-HT receptor subtypes as well, such as 5-HT_{1A} receptors [17]. Chemically, the 'classical' hallucinogens tend to fall into one of 3 categories: phenylethylamine derivatives, lysergamides, and tryptamine derivatives [18]. Mescaline is

the only hallucinogenic phenylethylamine so far identified in nature, but many synthetic analogs with similar activities and, in many cases, enhanced potencies, have been described [19]. In many instances, these synthetic analogs are close structural relatives of naturally occurring phenylpropanoids such as apiole, dillapiole, and myristicin, which occur in the essential oil fractions of many aromatic and spice plants. LSD, considered by many to be the prototype hallucinogen, has not been described from nature, but other lysergic acid amides with similar activity, if lesser potency, have been isolated from ergot, a parasitic fungus which grows on rye and other cereal grasses, and from the seeds of various genera of morning-glories, including *Argyreia* species, *Ipomoea* species, and *Rivea* species [20]. Historical evidence suggests that a hallucinogenic drink prepared from ergotized barley may have been consumed as part of the Eleusinian mysteries [21], while psychoactive morning-glory seeds, known to the Aztecs as *ololiuqui*, have been used for centuries in ceremonial rites in the highlands of Mexico and Central America [22]. Hallucinogenic tryptamine derivatives, which include the mushroom compounds, psilocybin and psilocin, as well as DMT and its closely related congener, 5-methoxy-DMT, are widespread in nature [23]. They are found as the active alkaloids in a variety of hallucinogenic preparations used by indigenous societies; DMT and 5-methoxy-DMT are the major active constituents of several New World snuff powders, which are prepared from a variety of botanical sources, primarily the genera *Anadenanthera* and *Virola*, and a DMT-containing admixture plant is responsible for the hallucinogenic properties of the well-known Amazonian drink, *ayahuasca* [24]. Recently, experimental ethnopharmacologists have found that volatilizing and inhaling the venomous exudate of certain toads (*Bufo alvarius* and possibly *Bufo marinaris*) can elicit a transient hallucinogenic response similar to pure 5-MeO-DMT [25]. It is likely that many other natural sources of active tryptamine derivatives remain to be identified, and some of these may well yield novel compounds.

5. Plants and natural products with putative serotonergic activity

Hallucinogens are not the only naturally occurring substances which can affect serotonergic functions, however. A cursory search of Napralert, the natural-product database maintained by the Program for Collaborative Research in the Pharmaceutical Sciences at the University of Illinois, Chicago, reveals a rather extensive list of plants which have been reported to affect serotonin, either by a direct effect on serotonin receptors or by influencing its synthesis, storage, reuptake, or release (Table 1). When Napralert is similarly queried for natural *compounds* with serotonergic actions, another extensive list results (Table 2). Only a few representative examples are presented in each table; the actual number of plants or compounds affecting serotonin is much more extensive than the examples cited. Thus, plants containing active compounds which can affect serotonergic functions should not be overlooked by medicinal chemists and pharmacologists seeking to develop new serotonergic agents, either for therapeutic applications, or for research purposes.

6. Plant hallucinogens and psychotherapeutic drug development

Hallucinogens, including those derived from plants, are a special case when discussed in relation to psychotherapeutic drug development. Except for a small cadre of radical psychiatrists and therapists who are generally regarded as out of the mainstream, the notion that

Table 1
Plant extracts with serotonergic activity

Plant name	5-HT agonist activity	5-HT antagonist activity	5-HT increase in vivo	5-HT depletion in vivo	5-HT releasing activity	5-HT uptake blockade	5-HT receptor blockade
Nitraria schoberi	X						
Uncaria sinensis	X	X					X
Angelica sinensis		X					
Azadirachta indica		X					
Chelidonium majus		X					
Davallia denticulata		X					
Eupatorium helianthemoides		X					
Gelsemium sempervirens		X				X	
Panax ginseng		X	X	X	X		
Piper methysticum		X					
Trianthema portulacastrum		X					
Centella asiatica				X			
Ginkgo biloba			X			X	
Artemisia siversiana					X		

Table 2
Natural compounds with serotonergic activity

Compound name	5-HT agonist activity	5-HT antagonist activity	5-HT increase in vivo	5-HT depletion in vivo	5-HT releasing activity	5-HT uptake blockade	5-HT receptor blockade
Corynantheine	X	X					
Geissoschizine methyl ether	X	X					
Hirsuteine	X						
Harmaline	X						X
Ibogaine	X						
Rhynchophylline	X						
Ajmalicine		X					
Cathinone		X			X		
Theanine					X		
Tabernanthine					X		
Glaucine, 7-hydroxy					X		
Anisodamine					X		
Chuanbeinone		X					
Deguelin		X					
Derrisic acid		X					
Ferulic acid		X					
Ginsenoside RB-1		X					
Gingerol		X					
Keramadine		X					
Xanthotoxol		X					
Palmatine			X	X			
Secalonic acid D				X			
Azadirachtin A			X				
Asiaticoside							X
Strychocarpine							X
Embelin						X	

hallucinogens may be a reasonable therapeutic option in certain situations is not an accepted tenet of Western medicine, despite an abundance of anecdotal evidence from shamanic traditions indicating that hallucinogens *can* frequently be efficacious in attenuating the causes (or at least the symptoms) of psychological disorders, if not physical illnesses [26]. While the potential therapeutic value of the psychedelic experience briefly attracted the attention of the psychiatric community several decades ago, efforts to develop a 'scientific' validation of hallucinogen therapy have been largely abandoned. Some have argued that this abandonment has taken place largely in response to political and societal pressures, and not because the psychedelic model of therapy has been investigated and found wanting [27]. Now some members of the psychiatric community are attempting to re-ignite the debate, arguing that the cathartic experiences which can, under the best of circumstances, be facilitated by hallucinogens may be a valid therapeutic modality [28]. Until consensus is reached on this issue (hopefully supported by some objective evidence), the contributions that hallucinogenic plants are able to make to psychotherapeutic drug discovery lie primarily in two categories given below.

6.1. Human psychopharmacology

Investigation of the human psychopharmacology of hallucinogens may provide investigators with pharmacological models of mental illnesses. The notion that the hallucinogenic experience is a 'model psychosis' dates from the middle of this century, when it was first suggested by Osmond and Smythies [29]. Osmond elaborated on his hypotheses by pointing out that, since many hallucinogens are structurally similar to neurotransmitters, metabolic defects, whether due to genetics or other causes, could lead to the endogenous synthesis of hallucinogenic substances capable of triggering some of the symptoms associated with schizophrenia, or mania, or other mental disorders. This theory has never been definitively disproven, nor can it be entirely discounted. Efforts to define a correlation between mental disease and the occurrence of hallucinogen-like substances in the blood or urine of psychiatric patients have had mixed results [30]. Nevertheless, the symptomatic profile associated with certain types of toxic psychosis, such as the resemblance between amphetamine psychosis and paranoid schizophrenia, indicate that biochemical causes may be at least partially implicated in some mental diseases. An examination of the pharmacological and biochemical mechanisms underlying the bizarre states triggered by hallucinogens may yet provide investigators with clues to possible metabolic factors contributing to mental illness.

The use of hallucinogens in therapeutic treatment regimens in non-Western cultural contexts, especially within shamanic traditions, is a second facet of their

human psychopharmacology which may prove useful to clinical investigators. While cross-cultural concepts of the etiology of mental and physical disorders, and the therapeutic regimens appropriate to those concepts, may seem exotic to physicians and psychiatrists trained in scientific medicine, there also exists abundant anecdotal evidence that these therapeutic modalities, including the ingestion of hallucinogenic plants, are sometimes effective [31]. Therefore, Western-trained psychiatrists may be well-advised to examine such practices with an open mind, in the hopes that shamanic practices may yield clues to more effective therapies [32]. Such an unbiased examination might well provide insight into procedures which would facilitate a more effective psychotherapeutic use of hallucinogenic agents within Western psychiatry and medicine.

6.2. *The elucidation of novel structures and mechanisms*

The second and third areas where investigations of naturally occurring hallucinogens can potentially contribute to the psychotherapeutic drug discovery process are quite closely linked: (1) phytochemical investigations of the active constituents of hallucinogenic or other psychoactive plants with a tradition of ethnomedical use can lead to the description of novel molecular entities; these novel molecules, in turn, may become structural templates, jumping-off points for medicinal chemists to develop analogs that may have desired activities, e.g., as analgesics or antipsychotics; and (2) novel structural entities are frequently associated with novel mechanisms of action, which may result from interactions with previously uncharacterized receptor populations, and/or from novel interactions with known receptor systems.

Salvia divinorum, a hallucinogenic member of the mint family (Labiatae) with a long tradition of ceremonial use in Mazatecan shamanism, provides one illustration of an instance where a novel structure may lead to a novel receptor system. The major psychoactive component of *Salvia divinorum* has now been shown to be Salvinorin A, a neoclerodane-type diterpene [33] whose activity has been demonstrated in both animal experiments and in human bioassays [34]. Apparently the compound is inactive when ingested orally, but when volatilized and inhaled produces a transient but profound dissociative response that is similar to the effect of the whole plant. The apparent extreme potency of the compound is also remarkable; via inhalation, doses as small as 50 μg elicit a threshold response, while the full spectrum of effects manifest between 250 and 500 μg. In receptor binding assays utilizing approximately 30 major neurotransmitter and hormone receptors, including the major serotonin receptor subtypes, the compound displayed no binding inhibition at concentrations of less than 10 μM [35].

Ibogaine, an alkaloid obtained from *Tabernanthe iboga*, a plant which is used ritually in initiation ceremonies and other rites of the Bwiti cult of West Africa, has received much attention in the popular media lately because of its putative ability to arrest or attenuate dependency syndromes associated with the abuse of opiates, cocaine, and other drugs of abuse [36]. Although ibogaine, an indole alkaloid, was first isolated early in this century, pharmacological investigations of its activity have been few. While it is putatively described as a hallucinogen, subjective reports of its effects indicate that they bear little in common with the response to 'classic' serotonergic hallucinogens such as LSD or psilocybin. These differences are also supported by its receptor profile; ibogaine does not display significant affinity for the known serotonin receptor subtypes, or any of the major CNS receptors with the exception of the κ-opiate receptor, for which it displayed a k_i of approximately 2 μM [37]. According to recent data, a metabolite of ibogaine, yet to be characterized structurally, has been isolated which displays sub-nanomolar affinity for κ-receptors (Sanchez-Ramos, personal communication, 1994). Ibogaine is only representative of a class of complex indole alkaloids that are particularly abundant in the Apocynaceae family, and it is likely that other naturally occurring alkaloids with related structures will also exhibit interesting CNS activity. In view of clinical and anecdotal evidence that ibogaine-like compounds may prove effective in interrupting the addiction syndrome, further investigations of the pharmacological properties of alkaloids in this class seem warranted.

Ayahuasca, a Quechua word meaning 'vine of the souls', is the appellation for a hallucinogenic beverage that is widely used by indigenous and mestizo healers throughout the Amazon Basin of South America [38]. The drink is prepared by boiling the crushed stems of a large liana, *Banisteropsis caapi*, together with the leaves of an admixture plant, *Psychotria viridis* (known as *chacruna* in the local vernacular). The component responsible for the hallucinogenic effect of *ayahuasca* is *N*,*N*-dimethyltryptamine (DMT), which is present in the leaves of *Psychotria viridis* at concentrations between 0.1 and 0.5% [39]. DMT itself is not orally active, however, due to inactivation by peripheral monoamine oxidase (MAO) in the liver and gut, and the pure compound must be taken parenterally, usually by being volatilized and inhaled [40]. The bark of the *Banisteriopsis caapi* vine, however, contains high levels of β-carboline alkaloids, including harmine, harmaline, and tetrahydroharmine, which are potent and selective inhibitors of MAO-A [41]. Thus, the combination of plants comprising the beverage –the admixture containing the active hallucinogen, DMT, and the vine containing potent MAO-inhibiting β-carbolines –provide a mechanism which accounts for the oral activity of the DMT-containing beverage: the β-carbolines in the brew inhibit peripheral MAO, thus protecting the DMT from

degradation and enabling it to cross the blood–brain barrier in an active form [42]. Both DMT and β-carbolines are widespread in the plant kingdom (both have been reported from over 25 separate families) [43,44], and experimental ethnopharmacologists have demonstrated that DMT/β-carboline concoctions prepared from a variety of botanical sources display oral activity that is similar to that of *ayahuasca*. [45]. These findings also raise the possibility that dietary factors may play a hitherto unsuspected role in the etiology of some mental disorders. DMT or similar compounds may be present in certain plants consumed as part of the diet; normally they would have no effect on the consumer, since they would be protected by peripheral MAO. If, however, the consumer should happen to have simultaneously taken an MAOI, or to have consumed a food in which β-carbolines were present, the psychoactive effects of the combination could become manifest. Such a response could be misdiagnosed as a psychotic reaction by medical personnel who were unaware of the contributing dietary causes. Thus, although DMT is a known compound with a relatively well-studied pharmacology, its oral activation by peripheral MAO inhibitors, as in *ayahuasca*, is a novel mechanism that remains relatively unstudied.

References

[1] Farnsworth, N.R., Akerele, O., Bingel, A.S., Soejarto, D.D. and Guo, Z.G., Medicinal plants in therapy, *Bull. WHO*, 63 (1985) 83–97.

[2] Farnsworth, N.R. and Morris, R.W., Higher plants: the sleeping giant of drug development, *Am. J. Pharm.*, 147 (1976) 46–52.

[3] Krieg, M., *Green Medicine*, Rand McNally and Co., Chicago 1964.

[4] Stoll, M., Essential oils. In: *Kirk-Othmer Encyclopedia of Chemical Technology*, 2nd. edn., Vol. 14, 1967.

[5] Jaffe, J.H. and Martin, W.R., Narcotic analgesics and antagonists. In: L.S. Goodman and A. Gilman (Eds.), *The Pharmacological Basis of Therapeutics*, 5th edn., McMillan Publishing Co., 1975, pp. 245–283.

[6] Kennedy, J., *Coca Exotica: The Illustrated Story of Cocaine*, Fairleight Dickenson University Press, Cornwall Books, 1985.

[7] Heffter, A., Ueber Cacteenalkaloide, *Ber. Deutsch. Chem. Ges.*, 29 (1896) 216–227.

[8] Jonas, H., *The Phenomenon of Life*, Dell Publishing Co., 1966.

[9] Nickerson, M. and Collier, B., Drugs inhibiting adrenergic systems and structures innervated by them. In: L.S. Goodman and A. Gilman (Eds.), *The Pharmacological Basis of Therapeutics*, 5th edn., McMillan Publishing Co., 1975, pp. 533–564.

[10] Seamon, K.B. and Daly, J.W., Forskolin: a unique diterpene activator of cyclic-AMP generating systems, *J. Cyclic Nucleotide Res.*, 7 (1981) 201–224.

[11] Joost, H.G., Habberfield, A.D., Simpson, I.A., Laurenza, A. and Seamon, K.B., Activation of adenylate cyclase and inhibition of glucose transport in rat adipocytes by forskolin analogues: structural determinants for distinct sites of action, *Mol. Pharmacol.*, 33 (1988) 449–453.

[12] Laurenza, A., Khandelwal, Y., De Souza, N.J., Rupp, R.H., Metzger, H. and Seamon, K.B., Stimulation of adenylate cyclase by water-soluble analogues of forskolin, *Mol. Pharmacol.*, 32 (1987) 133–139.

[13] Goodman, L.S. and Gilman, A. (Eds.), *The Pharmacological Basis of Therapeutics*, 5th edn., McMillan Publishing Co., 1975.

[14] Yano, I. and Takemori, A.E., Inhibition by naloxone of tolerance and dependence in mice treated acutely and chronically with morphine, *Res. Commun. Chem. Pathol. Pharmacol.*, 16 (1977) 721–734.

[15] Heikkila et al., Rotational behavior induced by cocaine analogs in rats with unilateral 6-hydroxydopamine lesions of the substantia nigra: dependence upon dopamine uptake inhibition, *J. Pharmacol. Exp. Ther.*, 211 (1979) 189.

[16] Makriyannis, A. and Rapaka, R.S., The molecular basis of cannabinoid activity, *Life Sci.*, 47 (1990) 2173–2184.

[17] Nichols, D.E., Oberlender and McKenna, D.J., Stereochemical aspects of hallucinogenesis. In: R.R. Watson (Ed.), *Biochemistry and Physiology of Substance Abuse*, Vol. III, CRC Press, Boca Raton, FL, 1991, pp. 1–39.

[18] Shulgin, A.T., Chemistry of psychotomimetics. In: F. Hofmeister and G. Stilke (Eds.), *Psychotropic Agents*, Vol. 55/III, Springer-Verlag, Berlin, 1982, pp. 3–29.

[19] Shulgin, A.T. and Shulgin, A., *PIHKAL: A Chemical Love Story*, Transform Press, Berkeley, CA, 1991.

[20] Chao, J.-M. and der Marderosian, A.H., Identification of ergoline alkaloids in the genus Argyreia and related genera and their chemotaxonomic implications in the Convolvulaceae, *Phytochemistry*, 12 (1973) 2435–2440.

[21] Wasson, R.G., Hofmann, A. and Ruck, C.A.P., *The Road to Eleusis: Unveiling the Secret of the Mysteries*, Harcourt, Brace and Jovanovich, New York, 1978.

[22] Ott, J., *Pharmacotheon: Entheogenic Drugs, Their Plant Sources and History*, Natural Products Co., Kennewick, WA, 1993.

[23] Smith, T.A., Tryptamine and related compounds in plants, *Phytochemistry*, 16 (1977) 763–766.

[24] Ott, J., op. cit.

[25] Davis, E.W. and Weil, A.T., Identity of a New World psychoactive toad, *Ancient Mesoamerica*, 3 (1992) 51–59.

[26] Dobkin de Rios, M., Peruvian hallucinogenic folk healing: an overview. In: R. de la Fuente and M. Weisman (Eds.), *Psychiatry: Proceedings of the Fifth World Congress of Psychiatry*, Vol 2.

[27] Shulgin, A.T. and Shulgin, A., op. cit., 1991.

[28] Grob, C.S., Psychiatric research with hallucinogens: what have we learned? In: C. Ratsch and J.R. Baker (Eds.), *Yearbook for Ethnomedicine and the Study of Consciousness*, Vol. 3, Verlag für Wissenschaft und Bildung, Berlin, 1994, pp. 91–112.

[29] Osmond, H. and Smythies, J., Schizophrenia: a new approach, *J. Ment. Sci.*, 98 (1952) 309–315.

[30] Barker, S.A., Monti, J.A. and Christian, S.T., *N,N*-dimethyltryptamine: an endogenous hallucinogen, *Int. Rev. Neurobiol.*, 22 (1981) 83–110.

[31] Andritzky, W., Sociopsychotherapeutic functions of ayahuasca healing in Amazonia, *J. Psychoact. Drugs*, 21 (1989) 77–89.

[32] Naranjo, C., *The Healing Journey*, Ballentine Books, New York, 1973.

[33] Ortega, A., Blount, J.F. and Manchand, P.S., Salvinorin, a new trans-neoclerodane diterpene from *Salvia divinorum* (Labiatae), Perkin Transactions I: Organic and Bio-organic Chemistry, *J. Chem. Soc.*, (1982) 2505–2508.

[34] Valdez, L.J., III, Hatfield, G.M., Paul, A.G. and Koreeda, M., Studies of *Salvia divinorum* (Lamiaceae), an hallucinogenic mint from the Sierra Mazateca in Oaxacaca, Central Mexico, Economic Botany, 41 (1987) 283–291.

[35] Siebert, D.J., *Salvia divinorum* and salvinorin A: new pharmacologic findings, *J. Ethnopharmacol.*, 43 (1994) 53–56.

[36] Cantor, M., Miracle Cure? Advocates say ibogaine ends the craving for dope, *Village Voice*, XXXV, June 5, 1990.

[37] Deecher, D.C., Teitler, M., Soderlund, D.M., Bornmann, W.G.,

Kuehne, M.E. and Glick, S.D., Mechanisms of action of ibogaine and harmaline congeners based on radioligand binding studies, *Brain Res.*, 571 (1992) 242–247.

[38] Schultes, R.E., The identity of the malpighiaceous narcotics of South America, *Botanical Museum Leaflets*, Harvard University, 18 (1957) 1–56.

[39] McKenna, D.J., Towers, G.H.N. and Abbott, F.S., Monoamine oxidase inhibitors in South American hallucinogenic plants: tryptamine and β-carboline constituents of Ayahuasca. *J. Ethnopharmacol.*, 10 (1984) 195–223.

[40] Shulgin, A.T., Profiles of psychedelic drugs: DMT, *J. Psychedelic Drugs*, 8 (1976) 167–168.

[41] Undenfriend, S., Witkop, B., Redfield, B. and Weissbach, H., Studies with reversible inhibitors of monoamine oxidase: harmaline and related compounds, *Biochem. Pharmacol.*, 1 (1958) 160–165.

[42] McKenna, D.J. and Towers, G.H.N., Biochemistry and pharmacology of tryptamine and β-carboline derivatives: a minireview. *J. Psychoact. Drugs*, 16 (1984) 347–358.

[43] Smith, T.A., 1977, op. cit.

[44] Holmstedt, B. and Lindgren, J.A. The simple β-carboline alkaloids, *Phytochemistry*, 19 (1980) 1573–1582.

[45] Ott, J., *Ayahuasca Analogs: Pangaean Entheogens*, Natural Products Co., Kennewick, WA, 1994.