Tabernanthe iboga: a Comprehensive Review

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Summary

Plants used in traditional medicine represent a priceless tank of new bioactive molecules. Currently plant based drugs are researched and formulated in modern framework in new ways of medicine. Many of the thousands of plant species growing throughout the world have medicinal uses, containing active constituents having significative pharmacological actions. The root of the *Tabernanthe iboga* plant (also known as eboga) is the most frequently cited source of ibogaine, and this plant contains 11 other known psychoactive constituents. Ibogaine is the active chemical found in the African Tabernanthe iboga root as well as several other plant species. It is a strong, long-lasting psychedelic used traditionally in a coming of age ritual but also known for its modern use in treating opiate addiction. Ibogaine has a long history of being used traditionally as a ceremonial, medicinal and spiritual tool in West Africa. Chemically, ibogaine is classified as a tryptamine, being a rigid analogue of melatonin, and is structurally similar to harmaline, another natural alkaloid and psychedelic agent. Ibogaine was first extracted from the *Tabernanthe iboga* root and it exerts primarily a stimulanting effect on the central nervous system. Ibogaine is a potent psychoactive substance showing also the unique property of significantly removing withdrawal symptoms and reducing cravings from substances causing chemical dependence. Recently, it has increasingly been used in western society as a unique therapy for detoxification from drugs and for other psychotherapeutic purposes.
Given the above evidences, this is a comprehensive review of *Tabernanthe iboga* leading to contribute to the knowledge of the pharmacology, phytochemistry and therapeutic aspects of its psychoactive constituent, ibogaine.

Introduction

Ibogaine is one of the psychoactive indole alkaloids found in the Central West African shrub, *Tabernanthe Iboga* or *Iboga*, a member of the family Apocynaceae. It is a perennial rainforest plant native to western central Africa. Normally, it grows to about 2 m in height but it may eventually grow into a small tree up to 10 m tall and it is cultivated by villagers as an ornamental shrub. It has small green leaves, its flowers are white and pink and its yellowish-orange fruits can be an elonged oval shape or a spherical shape. The yellow-brown coloured roots of *Tabernanthe iboga* contain a number of indole alkaloids, most notably ibogaine, which is found in the highest concentration in the root-bark. Thus, the root of the *Tabernanthe iboga* plant (also known as eboga) is the most frequently cited source of ibogaine, and this plant contains 11 other known psychoactive constituents.

The first botanical description of this tropical plant was made in 1889, later the major alkaloid was isolated from iboga rootbark, a crystalline compound which was called "ibogaine" or "ibogine". In west-central Africa where this plant grows (mainly Gabon, Cameroon, Congo) the bark of the root is chewed for different pharmacological or ritualistic purposes .(1) (2) (3).

Iboga has been used for centuries as a ceremonial sacrament in the rituals, initiation ceremonies and tribal nightly dances of several west African religions. The initiate, in the ibogaine-induced state, makes contact with the ancestral spirits and, after the ceremony, the initiate is reborn as an adult in the tribe having previous transgressions and illness removed in the initiation process. Traditionally, the root bark is scraped and dried to a yellowish-brown powder. The Iboga root may be eaten whole, or crushed and mixed with other ingredients, sometimes other psychoactive compounds, for example marijuana : the smoke generated represents the soul leaving the body and travelling to mix the ancestors. In small doses, Iboka is eaten for its stimulant effect to stay awake and alert while hunting, or to reduce fatigue, hunger, and thirst. It also reported to have aphrodisiacal properties.(4) (5).

The dosage for stimulant non-psychedelic effect is around two or three teaspoons for women, and three to five teaspoons for men. In larger amounts Iboka is taken for its hallucinogen effects, at this level the user falls in an intense, deep trance state called "dream-like state" or "waking-dreaming" characterized by retrieval of repressed memories as symbolic images. Past memories are relived primarily in a visual symbolic way but objectively, without their emotional contents, so past traumatic events and feelings are reduced to simple experiences.(6) (7) (8).

In short, ibogaine permits the exploration of user's subconscious to clarify his present personal issues through visual and conceptual symbols evoked. This process may be used in modern psychotherapeutic techniques.

In 1901 French pharmacologists found ibogaine to have an unusual type of excitatory effect in animals, they deduced ibogaine could produce hallucinations based on observations of animals' unusual behaviour. In addiction to ibogaine's psychological effects, it produces various dose-dependent physical effects : tremor, nausea and vomiting, ataxia, dystonia, light sensibility. (9).

At excessive levels, ibogaine causes convulsions, paralysis and death by arrested respiration.

Ibogaine was first used as a pharmaceutical product to Western medicine in the form of Lambarene, an extract of the Tabernanthe manii plant (10) containing 8 mg of ibogaine. In 1905 ibogaine was also indicated in the treatment of infectious diseases, depression, cardiac disorders, and it was observed the improvement of appetites, muscle tone and the general health condition in convalescence.(11).

In the 1940's were published a series of papers describing the pharmacological properties of ibogaine on isolated tissues and the cardiovascular system, so ibogaine extract was used as a tonic or stimulant above all by World War II athletes like a performance enhancing drug but it was removed from the market when the sale of ibogaine containing products were prohibited in 1966.(12).

The potential psychotherapeutic effects of ibogaine were studied for the first time by a Chilean psychiatrist, Dr. Claudio Naranjo, in the early 1960s. He found that ibogaine facilitated the resolution of repressed emotional conflicts because his patients relived their past experiences in an objective manner so they became able to confront their personal issues previously unapproachable (7). Around the same years, there was the casual discovery of ibogaine's anti-addictive effects by Howard S.Lotsof. He was not a scientist or a doctor but a simple based former heroin user who first took ibogaine in 1962 believing it a new recreational drug. He woke up the next morning realizing he no longer desired to seek heroin, in fact he remained free of the drug for years to follow (13). Some years later Lotsof started the promotion and development of ibogaine as an anti-addiction medication, he decided to form a company, NDA foundation, to better evaluate the drug's potential through experimental ibogaine treatments. (14).

At that time the possibility that a single molecule could treat dependence across different classes of abused drugs was considered revolutionary. In 1970, the FDA classified ibogaine as a Schedule I substances, so all non-research use was forbidden. Beginning in 1985, the use of ibogaine was patented for interrupting addiction to narcotics, cocaine and amphetamine, alcohol, nicotine and poly-drug dependency syndrome allowing patients to maintain a drug-free life style for at least 6 months after a single oral or rectal dose of ibogaine. A single administration of ibogaine, in fact, causes a massive reduction in the symptoms of drug withdrawal, a marked lowering in the desire to use drugs . Finally, the ibogaine's psychoactive nature helps many users to understand and resolve the issues behind their addictive behaviour. Ibogaine is not itself addictive so this substance may be taken a second time to help preserving a drug-free state, however it can be considered as simply as initial component in an overall rehabilitation strategy. The U.S. FDA and the National Institute for Drug Abuse approved the use of ibogaine to treat cocaine addiction, while researchers were also considering human trials for opiates and alcoholism. Although approved for clinical trials (trials on human) for the treatment of addiction in the US in the early 1990s, at present unceasing controlled clinical trials are underway to evaluate the safety of ibogaine and to test its anti-addictive efficacy. It is becoming increasingly clear, in fact, that there is a reasonable degree of risk associated with taking drug based on 12 recorded deaths occurred during the recorded treatment with ibogaine.
In conclusion ibogaine's psychoactive properties have been widely credited with helping drug-users to understand and reverse their drug addicted behaviour, moreover it has been suggest that the drug may have considerable potential in the field of psychotherapy, particulary as a treatment for the effects of trauma or conditioning.
Recent studies have revealed iboga alkaloids are active against human immunodeficiency type I virus (15), Candida albicans (16),and the tropical parasite Leishmania amazonesis (17).Furthermore it has been suggested by recent experiments iboga alkaloids' property to reverse the multi-drug resistance in human cancer cells.
Given the above evidences , this is a comprehensive review of *Tabernanthe iboga* leading to contribute to the knowledge of the pharmacology, phytochemistry and therapeutic aspects of its psychoactive constituent, ibogaine.

Pharmacological Actions :

Ibogaine can interact with different neurotransmitter systems, including k and μ opioid receptors, NMDA receptors, 5HT receptors, σ receptors, dopamine transporters and receptors, serotonin transporter and receptors, cholinergic receptors, calcium regulation and voltage dependent sodium channels, neuropeptides, purinergic and adrenergic receptors.
Ibogaine and its active metabolite noribogaine have multiple mechanisms of action in the nervous system because of their reported affinity for multiple targets. The evidences suggest that antiaddictive effects of ibogaine are mediated by its actions at several of these binding sites .

IBOGAINE ON DOPAMINERGIC SYSTEM

The effects of ibogaine on dopaminergic metabolism in mesolimbic areas (striatum, nucleus accumbens) are various and controversial : dopamine concentrations are reduced and dopamine metabolites (DOPAC and HVA) are increased after ibogaine administration of high concentrations, instead brain dopamine concentrations appear unchanged and dopamine metabolites concentrations are decreased after ibogaine administration of low concentrations or at long period after ibogaine administration. These findings suggest that ibogaine increases dopamine turnover shortly after administration. Ibogaine promotes the redistribution of dopamine from vescicular to cytoplasmic pools by inhibiting of vescicular monoamine transporters. The following rapid metabolism of dopamine by MAO could explain the decrease in tissue dopamine content and the parallel increase in its metabolites.(18).

Several studies report ibogaine acting at different neural sites through neurotransmitters or ion channels to modulate terminal dopamine release. Multiple interactions on presynaptic DA terminal produce receptor-induced stimulation and inhibition of DA release. Interactions and modulation between different various receptors on dopamine terminal are noted. Dopamine terminal release is stimulated by agonists to the sigma , NMDA, Ach, and 5-HT receptors. Dopamine terminal release is inhibited by kappa opioid agonists, and also 5-HT.
The effect of ibogaine on these receptor- responses is generally inhibitory . Furthermore, ibogaine increases dopamine release after cocaine or amphetamine administration.(19) .
Ibogaine also elevates plasma prolactin. Decreased release of dopamine in the hypothalamus may also explain the increased prolactin release following ibogaine administration.
Ibogaine changes the effects of abused drugs on dopaminergic system : the increase in mesolimbic dopamine produced by morphine or nicotine is reduced by ibogaine. A gender different response is observed when drugs like cocaine or amphetamine acting at dopamine presynaptic nervous terminal are followed by ibogaine administration. In female rats, amphetamine or cocaine induced increase in extracellular dopamine concentration, in both the striatum and nucleus accumbens, is enhanced by ibogaine but it decreases in male rats and mice (20).
Ibogaine, administered before morphine, inhibits the expected increase in extracellular dopamine concentration in the striatum, prefrontal cortex and nucleus accumbens, but the increase of dopamine metabolites is not changed ,therefore the activation of dopamine neurones is not altered by ibogaine.(21) (22).
Furthermore, ibogaine reduces the increase of dopamine in the nucleus accumbens after nicotine administration. However dopamine efflux is modulated by multiple neurotransmitters ,and ibogaine interacts with different neurotransmitter systems.
Ibogaine inhibits the development of drug-tolerance reversing the neuroadaptations to repeated drug-exposure: for example ibogaine increases the inhibition of adenylyl cyclase by serotonin, this is an effect opposed to the enhanced cAMP transduction associated with sensitization.(23).

IBOGAINE ON GLUTAMATERGIC SYSTEM

Ibogaine shows antagonist action on NMDA receptors supported by functional evidence: reduced glutamate-induced neuronal cell death, decrease of NMDA-activated hippocampal currents, reduction of NMDA mediated depolarization in motoneurons and prevention of NMDA induced convulsions. Ibogaine's NMDA non-competitive antagonism may explain its effects on drug dependence (24) (25) (26) (27).
The NMDA antagonist action of ibogaine is relevant to its antiaddictive properties. Many findings in fact demonstrate the interference of NMDA antagonists with tolerance and dependence to various abused drugs.

1. The neuroprotective effects of NMDA antagonists are extensively demonstrated, then ibogaine, like other NMDA antagonists, may protect against NMDA receptor-mediated neurotoxicity . NMDA antagonists in fact are effective in blocking the excitotoxic process induced by activation of NMDA receptors. These considerations are proved by many studies testing the ability of ibogaine to prevent glutamate-induced death of cerebellar neurons and to decrease this glutamate-induced neurotoxicity in a concentration dependent manner (28).
2. NMDA antagonist action of ibogaine might be used to treat other pathologies such as neurodegenerative disorders .

IBOGAINE ON OPIOID SYSTEM

Ibogaine on opioid system may enhance the activity of μ-receptors functionally without a direct agonist action at μ-receptors but acting at the level of second messenger signal transduction.

However the enhanced inhibition of adenylate cyclase is observed at maximal concentration of morphine, so it is possible that the ibogaine may prevent the tolerance to antinociceptive morphine effects without producing nociception directly. (29) (30).
It is also reported noribogaine enhances the antinociception of morphine.

IBOGAINE ON SEROTONIN SYSTEM
Ibogaine blocks serotonin presynaptic transporter, in fact both serotonin and ibogaine contain an indole ring in their structure, so the extracellular 5HT levels are increased . (31) (32) (33).
Ibogaine's hallucinogenic effect may involve altered serotonergic neurotransmission. It is reported ibogaine is an agonist at the $5HT_{2A}$ receptors.
Ibogaine may directly release serotonin and its affinity for serotonin transporter produces increase of extracellular level of 5HT but serotoninergic effects of ibogaine are relatively short lasting so serotonin would seem mediating only the acute behavioural effects of ibogaine.

IBOGAINE ON SIGMA RECEPTORS
Ibogaine shows high affinity for $sigma_2$ receptor inducing a concentration-dependent increase in intracellular calcium levels. The neurotoxic effects of ibogaine may involve the stimulation of sigma $_2$ receptor, which enhances the neuronal response to NMDA. (34) (35).

IBOGAINE ON ACETHYLCHOLINERGIC SYSTEM
Ibogaine is a non-selective and weak antagonist of muscarinic receptors, in fact the alteration of ibogaine-induced EEG and the increase of heart-rate are reversed by atropine. In literature is also reported the inhibitory effect of ibogaine on cholinesterase.(36) (37) (38).
Other studies instead report that ibogaine's affiniy at M1 and M2 receptors may mediate its tendency to lower heart rate.
Several studies indicate ibogaine decreases acetylcholine stimulation of nicotinic receptor by catecholamine release, and decreases dopamine release evoked by nicotine in the Nucleus Accumbens. Mah *et al.* suggest that ibogaine at high concentration acts at multiple sites and after its metabolism to lower levels has a selective action at the nicotinic receptor to inhibit catecholamine release. Therefore ibogaine produces non-competitive functional inhibition of the nicotinic acetylcholine receptor , possibly acting as an open channel blocker.

IBOGAINE ON NEUROPEPTIDES
Ibogaine increases neurotensin-like immunoreactivity (NTLI) in the striatum, substantia nigra, and nucleus accumbens , substance P in the striatum and in substantia nigra.(39).
These increases are blocked by D_1 antagonist. The NMDA receptors and D1 receptors are involved in the release of neurotensin by ibogaine , and neurotensin may contribute to the interaction of ibogaine and the dopamine system.(40).

NEUROENDOCRINE EFFECTS OF IBOGAINE
Various types of stressors can contribute to the development of drug dependence and of drug self-administration behaviour.(41) (42) (43) (44) (45).
The effects of stress on drug-seeking behaviour appear to be mediated by hormones of the hypothalamic-pituitary-adrenal (HPA) axis, particularly corticosterone.
Corticosterone can facilitate acquisition of drug self-administration behaviour similar to the effects of stress. (46) (47).
Corticosterone in fact is a major stress hormone of the HPA axis. Ibogaine administration in male rats (50 mg/kg i.p.) causes a sustained increase in corticosterone secretion that lasts for at least 2 hours. The effects of iboga alkaloids on plasma corticosterone could be mediated by different targets, including NMDA and $sigma_2$ receptors.

Chemical Properties and Pharmacokinetics

Ibogaine is an indole alkaloid with molecular formula $C_{20}H_{26}N_{20}$ and molecular weight 310.44. It has a melting point of 153° , a pK_a of 8.1 in 80% methylcellosolve, and it crystallizes as prismatic needles from ethanol. Ibogaine is soluble in methanol, ethanol, chloroform and insoluble in water. Ibogaine hydrochloride is soluble in water, methanol, ethanol, and insoluble in ether. Ibogaine is heat and light sensitive and it can spontaneously oxidize in solution. (48)

Ibogaine was first extracted from *Tabernanthe iboga* root. It was isolated and identified in 1901, but the structure of this alkaloid was established in 1957 by Taylor. The molecule exhibits the indole nucleus and a structure common to most hallucinogens. Chemically, ibogaine is classified as a tryptamine , being a rigid analogue of melatonin, and it is structurally similar to harmaline , another natural alkaloid and psychedelic agent.

After parental administration, ibogaine has been identified in blood and urine (humans) and in the liver, kidney and brain of laboratory animals. Ibogaine is subject to a significant "first pass" effect and it has a marked propensity to be deposited in adipose tissue reflecting its lipophilicity. Hough et al.(1996)(49) in fact reported that ibogaine showed high levels in fat for at least 12 hours after intraperitoneal administration in rats.

Ibogaine is extensively metabolized by the liver : the principal degradation pathway is O-demethylation at C12 giving the O-desmethylibogaine (also known as noribogaine or 12-hydroxyibogaine) pharmacologically active. Noribogaine has a longer half-life than ibogaine, therefore it is possible its involvement in long-term effects of ibogaine (Mash et al.,2000).(50). Noribogaine shows a superior side-effects profile compared to ibogaine because it does not produce adverse behavioural effects and it is less potent as a stimulator of HPA axis.

Differences in pharmacological responses to ibogaine may be attribuited to pharmacokinetic, rather than pharmacodynamic factors. Various pharmacological effects of ibogaine may be partially attributable to its metabolite. Some evidences suggest that an active principle responsible for one action may be more rapidly metabolized than compound involved in other actions. Alternatively different pharmacological effects of ibogaine may involve different neurotransmitters systems.(51)

Absorption : The estimated dose-dependent bioavailability of ibogaine after administering single oral doses suggests that its absorption and its first pass elimination are nonlinear, the greater bioavailability showed in female rats than in male rats is correlated with gender-related differences in absorption kinetics. (52)

Distribution : Ibogaine undergoes a substantial first-pass effect involving hepatic extraction, the highly lipophilic nature of ibogaine suggests that its prolonged actions could be due to its depot in adipose tissue serving as a reservoir with release and metabolism to noribogaine over a long period of time.(53).There are some evidences that platelets also might constitute a depot in which ibogaine is sequestered.(54).

Metabolism : Noribogaine represents the more important metabolite of ibogaine, it is produced through O-demethylation via CYP2D6 and it is pharmacologically active . This cytochrome is involved in the metabolism of several different pharmacological compounds , including opioids, neuroleptics, tricyclic antidepressant ,beta- blockers .(55).

The involvement of the CYP2D6, with its pharmacogenetic polymorphism in human population, suggests possible human pharmacogenetic differences in the metabolism of ibogaine: phenotypic CYP2D6 poor metabolizers, for example 5-10% of Caucasians, lack the gene coding the CYP2D6 so they have relatively less CYP2D6 activity to metabolize ibogaine to noribogaine, and they are more exposed to adverse interactions between ibogaine and other drugs normally metabolized by CYP2D6. (56) (57).

Noribogaine shows a reduced affinity for sigma-2 receptors so it produces no effect on cytosolic calcium concentration. Subjects with a low level of hepatic O-demethylase activity (slow metabolizers) are more susceptible to the cytotoxic effects of ibogaine than rapid metabolizers.

Escretion : Ibogaine and noribogaine are excreted via the renal and gastrointestinal tracts. In man, Ibogaine has a half-life of 7.5 hours, and some studies suggest the possibility of species differences

in its metabolism and clearance. The sequestration and the slow release of ibogaine from tissues, and the slow elimination of noribogaine might explain the extended effects of ibogaine.(58).
The short-half life of ibogaine suggests that its long-term effects may be attributable to its active metabolites. The slow release of ibogaine and its metabolites deposited in fat may contribute to their protracted actions.
It is important to remark the gender and genetic differences in behavioural responses and in metabolism of ibogaine to understand the increased sensitivity of females rats and the higher level of ibogaine in female brain after administration. It is possible that the elevated levels of circulating estrogen enhance the absorption of ibogaine from peripheral compartments into bloodstream. Gender dependent alterations in ibogaine pharmacokinetics could explain the marked sensivity of female rats to the behavioural, and neurochemical effects of ibogaine.(59) (60).
The reported species-differences in sensitivity to the neurotoxic effects of ibogaine could be correlated to different species-rate of ibogaine-demethylation to its less cytotoxic metabolite, noribogaine.

Toxicology

Ibogaine induces body tremors at moderate doses (20-40 mg/kg) , and Purkinje cells loss in the cerebellum at high doses (≥100 mg/kg). High doses of ibogaine also decrease heart rate without altering blood pressure.(61).
The LD50 value of ibogaine depends on the animals, and on the route of administration. Lotsof *et al.*(2002) (62) reported only three important human deaths related to ibogaine's intake : the autopsy on the first dead body showed a cardiac arrest so it was proved the contraindication in the use of ibogaine for patients with cardiovascular problems. The second death was related with the use of heroin during the ibogaine's treatment, heroin-ibogaine interaction could have been the cause of death because ibogaine increases the effects and toxicity of opiates (Popick and Glick, 1996).(6). The cause of third death was asphyxiation due to vomit obstructing airways, with liver failure as a secondary cause. These fatal cases have been considered isolated incidents, instead the recent reports of ibogaine neurotoxicity are more interesting and important for the general population.
A single intraperitoneal ibogaine dose of 100 mg/ kg causes a marked degeneration of Purkinje cells and activation of microglia in rat cerebellar cortex (63), however the neurotoxicity of ibogaine is reported to be dose-dependent.
O'Hearn and Molliver (1997) supposed that ibogaine produced Purkinje cell degeneration through protracted activation of the olivocerebellar projection ,but it was not directly toxic to Purinje cells. The neurohistology of rat cerebellum after acute exposure to 100mg/kg ibogaine was examined by O'Hearn and Molliver, various neurohistological biomarkers relieved in their studies showed loss of calbindin immunoreactivity, astrocytosis, and microgliosis , argyrophilic degeneration (degeneration selective silver-staining of dead neurons) . These findings confirmed the observed loss of Purkinje neurons in the cerebellar vermis . (64).
It was reported that a single acute dose (100mg/kg i.p. once) of ibogaine produced patches of dead cerebellar Purkinje neurons which became argyrophilic within a week after the ibogaine injection. (65).
These investigations also demonstrated the dose-response relationship between ibogaine dose and produced signs of Purkinje neurons damage.
O'Callaghan *et al.* (66) demonstrated that ibogaine increases expression of Glial Fibrillary Acidic Protein in the cerebellum and in other brain areas such as the striatum and hippocampus. Increased brain level of GFAP usually represents an indicator of neuronal damage in the brain.
Scallet *et al*.(1996) (67) reported that the initial target of ibogaine neurotoxicity is the activation of serotonin receptors in the forebrain. Ibogaine, in fact, has a strong structural similarity to melatonin and 5-HT, moreover 5-HT agonists induce a neuronal degeneration of cerebellar Purkinje cells or within frontal and medial thalamus similar to that produced by ibogaine.

However the consideration that ibogaine treatment does not induce a remarkable degeneration of forebrain structures, wealthy of 5-HT receptors, proves that the serotonergic stimulation is a damaging input only to the brainstem inferior olive neurons.
Several studies used other histological biomarkers, such as c-fos, to put in evidence the localization of brain cells activated by ibogaine : the c-fos expression, evoked after ibogaine administration, indicated the brain structures most affected by ibogaine. (68).
The expression of c-fos was greatly increased in the nuclei of the inferior olivary neurons and in cerebellar Purkinje neurons , these findings remarked that ibogaine -stimulated pathway contains endogenous neurotransmitters such as glutamate , aspartate able to produce neurotoxicity by excitotoxic effects, in this way the degeneration of Purkinje neurons may be explained. (69) .
It is indispensable in fact an intact excitatory input to the Purkinje neurons for the neurotoxic action of ibogaine. (70).
In conclusion the acute administration of ibogaine actives neurons in the inferior olive resulting in protracted release of glutamate from synapses in the Purkinje cells. This mechanism causes exitotoxic degeneration of the Purkinje cells in the cerebellum.
In other brain regions, as neocortex or hippocampal neurons ,was reported the ibogaine-induced increase of c-fos expression but the neurotoxicity was not observed . Ibogaine actives c-fos expression also in the thalamus and in the hypothalamic paraventricular nucleus which is an important neurosecretory regulator structure. PVN's cells are full with CRH neuropeptide so they regulate the neuroendocrine activity of pituitary . The influence of ibogaine on neuroendocrine functions could thus be explained. However this further property of ibogaine may be important to clarify its psychoactive action and to amplify its possible therapeutic actions.(71).
The neurotoxic effect of ibogaine actually appears to be also mediated by an agonist action at sigma-2 receptors .Sigma receptors are membrane proteins binding various psychotropic drugs, they are distribuited in the motor regions of the brain (substantia nigra, cerebellum, brainstem, motor nuclei), expressed in endocrine, immune, and reproductive systems, and present in liver, kidney and in several different tumoral cell lines.
Current evidences indicate that the chronic activation of sigma-2 receptors produces morphological changes and cell-death by necrosis or apoptosis. (72) (73).
The activation of sigma-2 receptors also induces the modulation of intracellular calcium increasing the cytosolic calcium concentration , this effect may explain the ability of sigma-2 receptors to produce cytotoxicity and apoptosis. Ibogaine acts as sigma-2 receptors agonist to deplete the store of calcium in the endoplasmic reticulum, it is reported that sigma-2 receptors' activation by ibogaine induces dose- and time- dependent changes in cellular morphology with DNA fragmentation and apoptotic cell death. It is supposed that ibogaine-activation of sigma-2 receptors produces both neurotoxicity and excitotoxicity caused by increased glutamatergic neurotransmission . Then ibogaine induces excitotoxicity though it is an NMDA-antagonist. The stimulation of sigma-2 receptors could contribute to other toxic effects of ibogaine, for example to its tremorigenic effect. The generation of tremors induced by ibogaine may be correlated to the high density of sigma-2 receptors found in brain motor control regions. However the neurotoxic actions of ibogaine are completely explained involving also other receptor sites. (74).
The reported neurotoxicity of ibogaine is an important impediment to the development of this drug an antiaddictive medication.(75) (76) (77). The neurotoxicity data show that therapeutic doses of ibogaine in rats (40 mg/kg i.p.) are very close to the minimum doses (50 mg/kg i.p.) required to produce cerebellar damage. Therefore, it is reported that the neurotoxic effects of ibogaine are clearly species dependent and dose related.
A synthetic congener of ibogaine , 18-methoxycoronaradine, has similar effects to ibogaine : it decreases extracellular dopamine levels in the nucleus accumbens, attenuates self-administration of abuse-drugs, but 18-MC is not tremorigenic and doesn't induce brachycardia or damage to Purkinje cells or toxicity in the general brain.(78) (79) (80).

This synthetic congener of ibogaine, 18-MC, could represent a possible clinical alternative to avoid human toxicity of ibogaine .
The anxiogenic effect of ibogaine was investigated using the elevated plus maze test in rodents. (81).
Recent studies report that ibogaine reduces the number of open arm entries in the elevated plus maze test in rats tested many hours after pre-treatment i.p. with ibogaine. It is possible the involvement of a long lasting ibogaine metabolite,since ibogaine's plasma half-time is about 1 hour in rodents.(82).
Ibogaine is also known to produce adverse behavioural effects in humans and animals. In humans, oral administration of ibogaine produces nausea, vomiting, dizziness, lasting motor incoordination and a waking dream state without loss of consciousness.(83) (84).
Administration of ibogaine to rats produces different transient motor behaviours such as tremors , forepaw treading, and ataxia. (85 -90).
Ibogaine causes a dose-related increase of tremors. The tremorigenic effects evoked by ibogaine are represented by tremors of the face, head, neck, and shivering movements of the trunk .After a high dose of ibogaine, about 10 mg/kg i.v., rats become to show abnormal posture, body sway, and a staggering locomotion. Ibogaine and noribogaine produce different behavioural effects even though having similar chemical structures. The motor actions of ibogaine are not mediated by central 5-HT mechanisms because ibogaine is less potent than noribogaine as an indirect 5-HT agonist, yet ibogaine evokes more potent tremorigenic actions. It is possible that ibogaine induces adverse motor effects involving NMDA or $sigma_2$ receptors, in fact ibogaine is more potent than noribogaine at these sites. (91-93).
There is an inherent level of risk with ibogaine therapeutic treatment. Al least 12 people are recorded as having died in connection with ibogaine or other iboga substances. The following factors have been identified as having caused death: pre-existing heart condition, using opiate when on ibogaine, using the rootbark or iboga extract because ibogaine HCl is statistically much safer, taking ibogaine without a clinical supervision. It is important to be medically tested and monitored before taking ibogaine. A basic level of physical and psychological screening is essential before ibogaine treatment. A blood test should be undertaken to check for liver abnormalities and heart function should be monitored by EKG constantly. Vomiting could be a serious problem during ibogaine therapy. Allergic reactions are not reported. Ibogaine shows the ability to potentiate other drug reactions : no heroin, no cocaine and no other drugs should be taken for a minimum of 12 hours before taking ibogaine, no methadone for a minimum of 24 hours, no stimulants should be taken for at least 24 hours prior to taking the main dose of ibogaine. Normal doses of benzodiazepines can safely be taken prior to ibogaine to assist in reducing anxiety of the client. the treatment setting is in fact very important for client to feel relaxed and to limit anxiety.
Assuming the client is sufficiently well to be treated, pure ibogaine HCl is typically administered at doses of around 10 mg per kilo bodyweight for men, and 9 mg/k for women. Indra iboga extract is approximately one quarter the strength of pure ibogaine HCl, and it induces more vomiting than the ibogaine HCl.
Ibogaine taking effects are shown after between 30 minutes and 2 hours. Withdrawal symptoms should be eliminated or easily manageable but therapeutic action is accompanied by ataxia, buzzing noise in the ears , feeling nauseous, sensation of body-pulsing, louder sounds, irritation to bright light . (94).

Treatment of Drug Dependence : multiple sites of ibogaine - action

In the majority of studies using rodent models, ibogaine has been suggested to have antiaddictive actions reversing behavioral effects of various abuse-drugs . Many of the addictive drugs have affinity to multiple neurotransmitter sites, and the addictive behaviours (cognition, reward, withdrawal, craving, sensitization) involve multiple neurotransmitter systems with their interactions, therefore the elevated extracellular dopamine reported represents only the primary

mediator of addictive-drug's responses. It is important to remark the interaction of multiple neurotransmitter systems and neuronal pathways in abuse-drugs responses to emphasize the radical importance of using ibogaine for drug-dependence treatment because of its revolutionary property to target multiple sites. Ibogaine inhibits the physiological and psychological effects of various drug of abuse : cocaine, morphine, amphetamine, heroin, alcohol, nicotine. These evidences suggest ibogaine's action explores complex multiple interactive neural system. Species and sex variations in ibogaine responsiveness may explain the reported variability in results and the difficulties in devising appropriate protocol in drug-dependence therapy. The mechanism of long-lasting effects of ibogaine is not very clear, it is difficult to correlate the protracted actions (reported for months in human) of ibogaine only to its pharmacokinetic properties . Then it is supposed that the simultaneous actions of ibogaine at multiple sites may induce a resetting of transmitter interactions so the presence of ibogaine is not necessary for a long term . Effects of ibogaine on changes in second messenger systems and gene expression in selected neuronal populations could be supposed as another possible mechanism of its long-lasting actions. (95) (96).

It is possible that antiaddictive effect of ibogaine is due to restoration of altered programs of gene expression and signal transduction .The involvement of coordinated programs of gene expression is critical for many brain functions, including long-term memory and drug addiction.(97).

Various animal and human studies show that ibogaine could modulate gene expression and the associated signal transduction mechanisms and restore disrupted neuroadaptive pathways due to drug-addiction. The pleasurable experience from abused drugs could alter the programs of gene expression. Addictive disorders may be characterized by aberrant pattern of gene expression that no longer respond to normal external stimulations. The interferences with dopamine pathways may not restore the altered function and plasticity in CNS of the drug-dependent individual. The initial trigger of the changes in gene expression may be different for the different drugs of abuse. It is reported that ibogaine could restore the behavioral and neurogenetic changes due to the treatment with cocaine. It is in fact known that cocaine is able to produce the alteration of specific genes in the brain by modulation of the expression genes tags(EPS).(98).

Abused drugs generally produce alteration of cAMP-dependent pathway that could influence the transcription of various genes trough promoter responsive sites (CRE element). (99).

Abused substances acting on cAMP-dependent pathway regulate the phosphorylation of specific transcription factor such as CREB, CREM, or ATF that promote the activation of genes with CRE like promoter responsive site.(100) (101) (102) .

The recent genetic studies indicate the possible link between genes and human disease, behaviour, or biology ,so, we could discover the potential gene expression responsible of individual vulnerable to drug dependency . The mapping of human genome could show gene products involved in addictions and the action of ibogaine.

It is reported ibogaine modulates various opiate actions in rats. Ibogaine increases opiate-induced analgesia (103), interferes with morphine tolerance(91), with the rewarding property of morphine self-administered (104) ,and with the adverse properties of opiate withdrawal (105) (106).

The ability of ibogaine to reverse drug-seeking behaviour is correlated to its action on multiple systems (107) (108). Activity of ibogaine on opiate, serotonin, dopamine, choline, glutamate, NMDA, sigma, monoamine transporters, hormonal systems could share in antiaddictive effect of alkaloid. The alteration of signal transduction systems correlated to behavioral symptoms of decreased control and compulsive use of abused drugs could be resolved by ibogaine through its multiple actions.(109).

Inhibitory action of ibogaine on drug addiction is associated to relevant side effects. Ibogaine reduces self-administration of abused drugs and the severity of opioid withdrawal showing ,also, anxiogenic actions and effects on learning and memory processes.(110,111,112,113) .

Thus, it is possible that therapeutic action of ibogaine on drug addiction is correlated to its interferences with learning and memory processes eliminating the cause of the disorder. The basis of drug-addiction, in fact, could be linked to past traumatic experiences or conditioning in

childhood of addicted individuals. Ibogaine could facilitate psychotherapy reducing the long times of psychotherapeutic process.(114). Therefore it is recommended that ibogaine not be administered in isolation, but as a simply stage of a wider therapeutic strategy.
Trauma is usually a single negative event, the memory of which and associated feelings are repressed. Conditioning is the process by which parents alter child's behaviour by repeatedly punishing certain acts. It is difficult treating the effects of both trauma and conditioning because the original traumatic event or act of conditioning is repressed, the individual has not conscious memory of it. Ibogaine treatment recalls repressed memories like a cognitive retrieval without emotional connection of the negative repressed experiences. In this way, ibogaine induces the users to open a frank discussion of personal unresolved problems for a period of at least a week after use.
Psychologically, the drug is essentially "oneirogenic" because it induces a dream state with the ego perspective intact. Dream behaviour induced by ibogaine serves to resolve stressed emotional conflicts of the past. Thus, ibogaine visions seem to respect the principles of dream analysis.
Furthermore, it is reported that ibogaine is most effective for older addicts, a casual study indicating that those over 35 have a better chance to resolve the drug using behaviour than those in their twenties. Melatonin and B vitamins could be useful after using ibogaine to maintain the drug's effect. Ibogaine is noted to have the ability to reset the learned behaviour customs of abused drugs users leaving them free from their compulsive needs. This effect lasts for a period of days or weeks, after this time could be shown feelings of anxiety, insecurity , disorientated state linked to the radical experience faced. Ibogaine resets many brain functions relating to drug usage and the possible return to abuse drugs could easily result in overdosing, and possibly death.

Ibogaine for Self-development and Iboga Visions

The use of ibogaine is not restricted to beat drug or alcohol dependence, it could be used also to access to more spiritual side of individual. Ibogaine could allow the users to become aware of unconscious processes that may be blocking their personal development. The dream-like visions open the access to unconscious in a relatively state of consciousness. The benefits of ibogaine 's adjunct treatment in psychotherapy are reported by numerous psychotherapists , most notable Chilean psychiatrist Claudio Naranjo.(115).
Ibogaine gives people mental insights into repressed aspects of their psyche without emotional connection. Thus , the use of ibogaine could represent the first step to start a deep personal transformation. Iboga visionary experiences are generally characterized by an *oneirophrenic* phase and a following *processing* phase of many hours, although there are variations from person to person. The *oneirophrenic* phase or *dream-creating* phase lasts several hours and usually consists of the user experiencing dream-like visions with closed eyes. Dreamlike visions normally cease once the eyes are opened. Experience also indicates that for many the cathartic process induced by ibogaine continues long after taking the drug. Ibogaine visions invariability contain personal material, feelings and sensations associated with childhood and early life but represented in a typical symbolic way. The *processing* phase follows once the first stage is concluded. This phase is characterized by high levels of mental activity to realize the interiorized process. Thus, personal material revealed in the first phase is assimilated and interpreted.
The *oneirophrenic* phase typically starts 1-2 hours after taking the main dose of ibogaine ,and the *processing* phase about 3-6 hours later, usually lasting for between 8 and 14 hours.
Thus, the use of ibogaine is not restricted to beat drug or alcohol dependence. Individuals could use ibogaine also to access to the spiritual side of their nature or to overcome a psychological block.

Conclusion

Plants used in traditional medicine represent a priceless tank of new bioactive molecules. Currently plant based drugs are researched and formulated in modern framework in new ways of medicine. Many of thousands of plant species growing throughout the world have medicinal uses, containing active constituents having significative pharmacological actions.

Ibogaine is the active chemical found in the African *Tabernanthe iboga* root as well as several other plant species. It is a strong and long-lasting psychedelic used traditionally in a coming of age ritual but also known for its modern use in treating opiate addiction. Ibogaine has a long history of being used traditionally as a ceremonial, medicinal and spiritual tool in West Africa.

Ibogaine primarily exerts a stimulating effect on the central nervous system, it is a potent psychoactive substance showing also the unique property of significantly removing withdrawal symptoms and reducing cravings from substances causing chemical dependence. Recently, it has increasingly been used in western society as a unique therapy for detoxification from drugs and for other psychotherapeutic purposes.

Ibogaine could represent a novel approach to addiction treatment because it resets the neural and behavioural alterations due to drugs addiction acting on the origin of the disorder directly. Thus, ibogaine therapy needs a more intimate relationship between the patient and the clinicians. Ibogaine shows various advantages over traditional addiction treatments (116) : absence of fear during the detoxification and the ability of addicts to control their need of using drugs.

The significant benefits of ibogaine need further studies and clinical research to evaluate also the risks of this compound for general use. There are many problems for ibogaine development because it necessities the participation of pharmaceutical companies. The problems that drugs companies have to make ibogaine to mass market are various : firstly, ibogaine is a drug derived from natural sources so the patent options are more limited and this matter reduces the financial return of industries. Secondly, ibogaine is not a maintenance drug and it is usually administered only once. Thus, the development of this novel medication is not considered sufficiently advantageous for pharmaceutical companies. Furthermore, there are public-relations problems for industries when developing medications for socially marginalized groups such as drug addicts.

Politics of self-serving interests and dubious moral worth could continue to obstruct the progress of science.

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