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Pharmacology, Biochemistry and Behavior 75 (2003) 501–512
PHARMACOLOGY BIOCHEMISTRY AND BEHAVIOR
www.elsevier.com/locate/pharmbiochembeh

Review article

# Plants and the central nervous system

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Received 2 November 2002; received in revised form 20 March 2003; accepted 31 March 2003

**Abstract**

This review article draws the attention to the many species of plants possessing activity on the central nervous system (CNS) In fact, they cover the whole spectrum of central activity such as psychoanaleptic, psycholeptic and psychodysleptic effects, and several of these plants are currently used in therapeutics to treat human ailments.

Among the psychoanaleptic (stimulant) plants, those utilized by human beings to reduce body weight [*Ephedra* spp (Ma Huang), *Paullinia* spp (guaraná), *Catha edulis* Forssk (khat)] and plants used to improve general health conditions (plant adaptogens) were scrutinized.

Many species of hallucinogenic (psychodysleptic) plants are used by humans throughout the world to achieve states of mind distortions; among those, a few have been used for therapeutic purposes, such as *Cannabis sativa* L., *Tabernanthe iboga* Baill and the mixture of *Psychotria viridis* Ruiz and Pav and *Banisteriopsis caapi* (Spruce ex Griseb.) C.V Morton Plants showing central psycholeptic activities, such as analgesic or anxiolytic actions (*Passiflora incarnata* L., *Valeriana* spp and *Piper methysticum* G Forst.), were also analysed.

Finally, the use of crude or semipurified extracts of such plants instead of the active substances seemingly responsible for their therapeutic effect is discussed.
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*Keywords:* Medicinal plants; Plant adaptogens; Khat; *Ephedra* spp.; CNS plants; Guaraná; Ayahuasca; Iboga; *Passiflora*; *Valeriana*; *Kava-kava*

## 1. Introduction

Mind-altering drugs, especially plants, have always fascinated human beings Surrounded by mystic superstitions, magic thoughts and religious rituals, they have always occupied man's attention Among the plants used by humans, those able to alter the conscience and the sensorium have drawn special consideration In fact, due to their astonishing effects, the psychodysleptic drugs (according to the Delay and Deniker, 1961, nomenclature), also called hallucinogenic drugs, have occupied much of the researchers' time, directed most of their thoughts and efforts towards attempts to understand their mechanism of action, and, hence, to understand human behavior, thoughts, humor, sensations, etc.

However, the challenge of trying to unravel the mechanisms of action on mood, humor, cognition, sensorium, etc., led to an inconvenience: to ignore, or to face as low priority, the fact that plants could also have beneficial properties to treat mental disease and some psychic ailments Furthermore, as most of the plants were first used by the so-called primitive cultures, their occasional use by the White occidental culture was relegated to a second plan, being considered as sorcerer's therapeutics In this respect, it is pertinent to quote a sentence from the first description in 1651 of a Mexican hallucinogenic plant (ololiuqui): "A thousand visions and satanic hallucinations appeared to them" (Hofmann, 1982).

A perverse result of such posture was a neglect of and probably more, a disdain, for all kinds of therapeutics based on plants.

Thus, until recently, very little attention was given by the scientific community to the benefits, as accepted by folk medicine, of the therapeutic usefulness of plants endowed with psycholeptic and psychoanaleptic (Delay and Deniker, 1961) properties.

Fortunately, this bad tide has recently turned due to several reasons, among them the wrong belief that plants, by originating directly from nature, must be less toxic than synthetic drugs Another important aspect for this turning point was the realization by the pharmaceutical industry that plants, after all, could be a good business as more and more

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0091-3057/03/$ – see front matter © 2003 Published by Elsevier Science Inc.
doi:10.1016/S0091-3057(03)00112-6

people were prone to look for this unconventional form of therapy For example, Eisenberg et al (1993) found that among American citizens, between 20% and 28% used alternative treatments for central nervous system (CNS) symptoms such as insomnia, headache, anxiety and depression; 3% of those patients had used herbal medicines.

If one wants to go down to the bottom of the problem, it is worth mentioning the fascinating study by Dossaji et al (1989) They describe the unusual feeding behavior in wild chimpanzees consuming leaves of plants of the *Aspilia*, *Lippia*, *Hibiscus* and *Rubia* genera; these are plants used by humans for medicinal purposes Female chimpanzees used to swallow *Aspilia* leaves more often than males (Dossaji et al., 1989).

In the same line of reasoning, the words of Schultes (1990) also apply here:

> People whom we have to consider members of less-advanced societies have consistently looked to the Plant Kingdom ... for the betterment of life.Should we as chemists, pharmacologists and botanists—with so many and varied means at our disposal—not take a lesson from them?

This review article deals with plants possessing psychoanaleptic, psycholeptic or psychodysleptic effects on the CNS However, because of the huge amount of plants belonging to these categories, we decided to select a few plants and to focus our attention on them, mostly concerning their clinical use Furthermore, plants that had been thoroughly studied in the past and were the object of many published articles, as in the cases of, for example, *Papaver somniferum* L., *Coffea arabica* L., *Cannabis sativa* L., *Theobroma cacao* L., *Erythroxylum coca* Lam., *Thea* spp., *Rauwolfia serpentina* Benth et Kurz., *Hypericum perforatum* L., *Panax ginseng* C.A Mey., *Piper methysticum*, *Ginkgo biloba* L., to mention just a few ones, will not be approached.

In order to attain this goal, we have searched articles published since 1995 in *Planta Medica* (George Thieme Verlag), *Phytotherapy Research* (Wiley), *Fitoterapia* (Elsevier), *Journal of Ethnopharmacology* (Elsevier) and *Phytomedicine* (Gustav Fischer), and scattered studies in other journals and books.

For further discussion on the therapeutic use of medicinal herbs, see Craig (1997), Wong et al (1998), Nwosu (1999), Briskin (2000), Elvin-Lewis (2001) and Phillipson (2001).

## 2. Psychoanaleptic (stimulant) plants with emphasis on anorectic or weight-reducing properties

Nature provides human beings with a myriad of plants possessing CNS stimulant properties For example, in a recent book on medicinal plants from Brazil (Mors et al., 2000), 103 species are listed as having excitatory, analeptic, anti-exhaustion and aphrodisiac effects.

Many of the plants endowed with CNS stimulant effects, as a rule, synthesize substances containing the phenylethylamine or xanthine moieties, which are able to enhance catecholaminergic effects and/or to act on adenosine receptors Consequently, they possess, besides many other effects, weight-reducing properties either by decreasing food consumption (anorectic effect) or by increasing energy expenditure (thermogenic effect) Because of these pharmacological properties, some plants are being widely used in weight-reducing therapeutics.

It is known that a sizeable amount of people in certain countries is overweight [body mass index (BMI) between 25% and 30 kg/m$^2$] or obese (BMI $>30$ kg/m$^2$) For example, in the United States these values reach 25–34% of the population (Kuezinarski, 1992) and in England the BMI >25 varies from 29% for women to 43% for men (Glenny et al., 1997) Obesity is considered an important public health problem because of its morbidity, mortality and associated diseases (Atkinson and Hubbard, 1994; Bray, 1995).

Among the factors contributing to obesity, food ingestion and energy expenditure are especially recognized as targets for pharmacotherapy strategies (Nappo and Carlini, 1994;Yanovski and Yanovski, 2002) When a drug induces a decrease in food ingestion (or energy intake) it is called anorectic; if it stimulates energy expenditure it is a thermogenic drug.

Inhibition of appetite or promotion of satiety, consequently decreasing food ingestion, is a common approach used by medical doctors who prescribe substances acting on the catecholaminergic and/or serotoninergic systems in CNS Mazindol, phenproporex, phentermine, diethylpropion, phenylpropanolamine and sibutramine are examples of such substances (Silverstone, 1992).

It is well known that plants are also used in the treatment of obesity According to Moro and Basile (2000), such plants may have direct or indirect actions on reduction of body weight.

Directly acting plants are those whose effects are mediated through appetite modulation and/or by increasing energy expenditure Plants with indirect actions would reduce weight by promoting diuresis, defecation or a CNS sedation (or even anxiolytic effect), as anxiety accompanies and promotes overeating.

The following are examples of plants acting directly on the CNS by inducing an anorectic effect.

### 2.1. Ephedra sinica Stapf and other Ephedra spp.

Ma Huang, the name by which the ephedra plant has been known in China since ancient times, synthesizes ephedrine and pseudoephedrine, phenylethylamine type of substances that possess CNS stimulant effects similar to those of amphetamines (Glennon and Young, 2000) although less prominent Peripherally, it acts on $\alpha$- and $\beta$-adrenergic receptors Centrally, ephedrine promotes the release and inhibits the uptake of noradrenaline, resulting

in a decrease of food intake and promotion of satiety, via hypothalamic centers controlling appetite (Astrup et al., 1995; Carek and Dickerson, 1999).

Furthermore, ephedrine enhances thermogenesis, increasing energy expenditure that also helps in weight reduction; it is believed that the thermogenic effect of ephedrine is because of its peripheral stimulation of β receptors (Dulloo, 1993; Carek and Dickerson, 1999).

As a CNS stimulant, ephedrine can induce insomnia, nervousness, tremors and anxiety Long-term therapy with ephedrine in higher doses may cause psychotic episodes such as paranoia, hallucinations and other mental disturbances (Herridge and A'Brook, 1968; Poston et al., 1998; Whitehouse, 1987) Death has been reported following chronic use of Ma Huang extract (Theoharides, 1997).

In a telephone survey conducted in the United States, 1% of 14,649 individuals reported use of ephedra products for weight loss purposes (Blanck et al., 2001) Ephedrine and pseudoephedrine have also been used by athletes for performance enhancement; for this reason, the International Olympic Committee has banned their use (Gill et al., 2000).

### 2.2. Guaraná (Paullinia sp.)

The famous Brazilian guaraná has the botanical name of *Paullinia cupana* var *sorbilis* (Mart.) Ducke The United States Pharmacopoeia describes guaraná under two names: *P cupana* Kunth and *Paullinia sorbilis* Martius Nowadays, it is recognized that there is only one species with two varieties: *P cupana* var *cupana* and *P cupana* var *sorbilis* (Lleras, 2002).

Many qualities are attributed to guaraná, from a stimulant to an aphrodisiac The guaraná seeds contain caffeine (2.5–5.0%) as well as theophylline and theobromine in small amounts; they also contain large quantities of tannins.

Through its methylxanthine content, guaraná is able, among other effects, to block adenosine receptors and to inhibit phosphodiesterase Because of the latter it enhances actions of noradrenaline, which is released from stores by ephedrine (Dulloo, 1993; Carek and Dickerson, 1999) Therefore, the existence of commercially available herbal mixtures containing Ma Huang and guaraná as active ingredients is not surprising One of these mixtures, in a randomized, double-blind, placebo-controlled study, effectively promoted weight loss and fat reduction of overweight men and women (Boozer et al., 2001) Its effects were accompanied by stimulatory symptoms characteristic of ephedrine and caffeine The "synthetic" or "chemical" counterpart of this herbal mixture (Ma Huang plus guaraná), is the ephedrine/caffeine association, which has also been proved effective In fact, Molnar et al (2000), in a double-blind, placebo-controlled trial, showed that the mixture was an effective and safe product for the treatment of obesity in adolescents.

The stimulant effects of guaraná go beyond its anorectic effect In fact, administered chronically, it increased the physical capacity of mice subjected to stressful situations such as forced swimming and partially reversed the amnesic effect of scopolamine, as measured through a passive avoidance test in rats and mice (Espínola et al., 1997) There was also a tendency of the rats chronically treated with guaraná to better maintain the memory of a Lashley III maze path (Espínola et al., 1997) An antioxidant effect was also shown since, even at low concentrations, guaraná inhibited the process of lipid peroxidation probably due to its tannin content (Mattei et al., 1998) It is interesting that rats treated with caffeine in a dosage similar to the amount found in the guaraná extract did not show any betterment of their physical and mental performances; that is, caffeine did not present an antifatigue effect as the plant did (Espínola et al., 1997) It was then suggested that those effects of the guaraná extract, on the physical performance as well on the memory of animals, could be due to substance(s) other than caffeine Tannins present in high amounts (16.0%) in the guaraná powder utilized may be responsible for such activity (Espínola et al., 1997; Mattei et al., 1998).

Other caffeine synthesizing plants are also used as antiobesity medicines; for example, the Chinese oolong tea (*Thea sinensis* L.) (Han et al., 1999) and the South American erva-mate tea (*Ilex paraguariensis* A St.-Hil.) (Martinet et al., 1999; Mors et al., 2000), are used worldwide as health drinks and for obesity prevention Saponins and catechins present in green tea extracts seem to be responsible, together with caffeine, for the antiobesity effects in animals (Han et al., 2001; Murase et al., 2002) and in humans (Chantre and Lairon, 2002).

### 2.3. Plant adaptogens

The term adaptogen was first coined by Lazarev (1947), meaning a substance that can develop a state of raised resistance, enabling an organism to cope with different kinds of stressful situations (Wagner et al., 1994) This concept is derived from the "general adaptation syndrome" advanced by Hans Selye (1937, 1938), and proposes that an organism when facing a stressful situation goes through three physiological phases: (1) alarm, (2) resistance and (3) exhaustion.

According to this syndrome, an organism has a limited capacity to cope with environmental aggression, and this capacity may decline with the continuous exposure to such an aggression, resulting in health disturbances and disease.

An adaptogen, through chronic administration, would then be able to adapt the organism to the unhealthy environmental aggression and make the organism resistant to the ill effects of that aggression (Panossian et al., 1999).

According to Breckhman and Dardymov (1969), an adaptogen must have the following properties:

1. show a nonspecific activity, i.e., increase in power of resistance against physical, chemical or biological noxious agents;
2. have a normalizing influence independent of the nature of the pathological state;

3. be innocuous and not influence normal body functions more than required.

It is accepted that adaptogen plants, when chronically used, are able to increase the animal's capacity to endure physical, chemical or environmental aggressions.

As a consequence, there is a general improvement in health conditions, which can be manifested, among other things, through the betterment of cognitive functions (such as learning and memory capacities) and an increase in quality of sleep and sexual performances (Breckhman and Dardymov, 1969; Baranov, 1982; Carlini, 1989).

On the other hand, it is doubtful whether these beneficial effects are directly mediated through the CNS, it being very likely that the endocrine system plays a major role (Wagner et al., 1994) However, a list of the main adaptogen plants is included in this review article, as they have effects that involve, albeit indirectly, improvement of several CNS functions:

*Eleutherococcus senticosus* (Rupr and Maxim.) Maxim (Fulder, 1980; Davydov and Krikorian, 2000).
*Bryonia alba* L (Panossian et al., 1997).
*Schisandra chinensis* (Turcz.) Baill (Hancke et al., 1999).
*P ginseng* (Baranov, 1982; Gillis, 1997; Attele et al., 1999; Vogler et al., 1999).
*Withania somnifera* (L.) Dunal (Dhuley, 2000, 2001; Singh et al., 2001).
Rasayana herbs (Rege et al., 1999).
*Rhodiola rosea* L (Kelly, 2001).

### 2.4. Catha edulis Forssk

This bush-like plant, or "khat," has been known for centuries in East Africa, the Middle East, including Ethiopia, Tanzania and North Yemen The chewing of khat leaves is the usual way by which people living in those areas use the plant (Nencini et al., 1986) Recently, this habit has reached other parts of the world (Al-Motarreb et al., 2002).

Khat induces a clear anorectic effect (Zelger and Carlini, 1980), together with euphoria, excitation and cheerful sensation (Nencini et al., 1986) These effects are produced mostly by phenylpropanolamines present in the leaves: cathinone (*S*-α-aminopropiophenone), cathine [(−)-1*S*,2*S*-norpseudoephedrine] and (−)-IR,2*S*-norephedrine These substances have pharmacological properties similar to those of D-amphetamine (Zelger et al., 1980), as they provoke the release and inhibit the uptake of dopamine in CNS (Zelger and Carlini, 1981).

A recent review on the medical and sociological aspects of khat use is found in Al-Motarreb et al (2002).

### 2.5. Other psychoanaleptic plants

The plants listed below have been extensively studied, and merited the publication of excellent review articles.

Therefore, to discuss them would be beyond the scope of the present work; instead, the reader will be referred to a few pertinent articles on these plants:

*E coca* (Holmstedt and Fredga, 1981; Johanson and Fischman, 1989; Karch, 1999);
*H perforatum* (Bombardelli and Morazzoni, 1995; Deltito and Beyer, 1998; Hippius, 1998; Barnes et al., 2001; Whiskey et al., 2001; Mendes et al., 2002); also referred to in the studies presented in two recent symposia on the plant and published in *Pharmacopsychiatry* June 1998;31 (Suppl I):1–60 and *Pharmacopsychiatry* 2001;34(Suppl I):1–123.

## 3. Plants with psychodysleptic properties

Hallucinogens, psychotomimetics, psychometamorphics, entactogens psychotogens, psychedelics, psychodysleptics, etc., are all synonymous with the word phantastica used by L Lewin in 1924 A brief description of the effects of these drugs follows:

- on cognition: interference with memory, attention, reasoning and orientation, all important cognitive functions;
- on sensorium: illusion, delusion, depersonalization, lack of contact with reality and sensorial alterations such as loss of sensitivity to corporal movements and posture, and loss of temporal and space discriminations.

For an in-depth discussion on hallucinogenic effects, see Abraham et al (1996).

Nature was extremely generous to provide men, for good or evil, with literally hundreds of plants endowed with chemical substances able to alter brain functions leading to the abovementioned marked mental alterations In the incomparable book *Plants of the Gods: Origins of Hallucinogenic Use*, Schultes and Hofmann (1979) listed 91 such plants, belonging to 44 botanical families occurring all over the world, used by men mostly to attain altered states of mind Of those families, the Solanaceae are present with 12 genera (14 species), Cactaceae with 10 genera (10 species) and Leguminosae (Fabaceae) also with 10 genera (10 species) Recently, four more hallucinogenic plants were described (De Smet, 1996) in addition to those listed in the book *Plants of the Gods*.

In spite of all these different botanical families, genera and species occurring in most parts of the world, their hallucinogenic active principles do not vary much With the exception of the cannabinoids from *C sativa*, all other known active principles have nitrogen and possess one of three chemical moieties: phenylethylamine (typical example: mescaline), indole [tryptamines, ergolines, β-carbolines (typical examples: psilocybin, dimethyltryptamine, harmaline)] or the anticholinergic tropane esters (atropine, escopolamine), although not "true hallucinogens" as LSD-25, psilocybin,

etc., still are able to produce psychedelic experiences (Dilsaver, 1988; Marken et al., 1996; Müller, 1998).

There is not much left to discuss on hallucinogenic plants after the masterly studies, performed during the second half of the 20th century, by Richard Evans Schultes from the Botanical Museum of Harvard University, USA; Albert Hofmann, from Sandoz Laboratory, Switzerland; Bo Holmstedt from Karolinska Institute, Sweden; and N.R Farnsworth from the University of Pittsburgh, USA The readers are referred to some of their excellent papers to obtain more information (Holmstedt and Lindgren, 1967; Farnsworth, 1968; Schultes and Holmstedt, 1968).

In the present article, therefore, we will comment mostly on studies of the emerging therapeutic use of three hallucinogenic plants: *T iboga* and Ayahuasca (a mixture of *Psychotria viridis* and *Banisteriopsis caapi*).

For further discussion on the medicinal use of hallucinogens, see "Therapeutic use of hallucinogens," *Journal of Psychoactive Drugs* 1998;30(4).

### 3.1. Ayahuasca (hoasca in Portuguese): B caapi and P viridis

In the beginning of the 20th century, a new religion appeared in Brazil, utilizing hoasca (also called iagê and caapi), the beverage consumed by certain Indians in the Amazon area (Costa and Faria, 1936; Lopes, 1934) The consumption of hoasca is established as religious cults in the cities of northern Brazil, under the names of Santo Daime, União do Vegetal and other smaller sects and is spreading to southern Brazilian cities and to other countries (Grob et al., 1996; Casenave, 2000).

Hoasca is particularly interesting, as its pharmacological activity is dependent on a synergism between two plants, *P viridis* and *B caapi* The latter contains β-carboline alkaloids mainly harmine and harmaline, whereas *P viridis* has *N*,*N*-dimethyltryptamine (DMT) in it (Liwszyc et al., 1992; Callaway et al., 1994a).

The psychic effects of hoasca result from the inactivation of MAO present in the intestines, thus protecting DMT from oxidative deamination and enabling it to reach the brain through the blood stream (McKenna et al., 1984) Actually, it is quite extraordinary that the Indians, obviously without any concepts of chemistry and not being "clinical pharmacologists," managed in the past to discover how to use such a plant mixture.

Therefore, the route of administration either of hoasca or of pure DMT is essential to obtain the psychic effects The latter is a potent, although short-acting, hallucinogenic agent when smoked or used intravenously, but it is devoid of action by the oral route (Strassman, 1996) Nonetheless, DMT can act orally when intestinal MAO is inhibited, as it actually happens on drinking hoasca.

Concerning the possible mechanism of DMT action, several studies yielded evidence that brain serotonin receptors are involved; thus, DMT (and other indole hallucinogenic agents) acts as agonist at 5-$HT_2$ receptors (McKenna and Peroutka, 1989; Johnson et al., 1990; Grella et al., 1998) and its effects can be blocked by ketanserin, a 5-$HT_2$ antagonist (Winter and Rabin, 1988; Arnt, 1989) An agonistic effect of DMT on 5-$HT1_a$ receptors was also postulated (McKenna et al., 1990; Deliganis et al., 1991) However, a blockade of these receptors with pindolol significantly enhanced the effects of DMT (Strassman, 1996).

It has also been shown that chronic hoasca users have an increased number of transporter sites for 5-hydroxtryptamine in the platelets (Callaway et al., 1994a).

In short, DMT effects are related to its actions on the serotonergic system, as it acts on at least three points of this system: 5-$HT_2$, 5-$HT1_a$ receptors and 5-HT-protein transporter.

In one excellent study, Grob et al (1996), by interviewing 15 followers of the União do Vegetal church, described that 11 (73%) of them were moderate to severe alcohol users previous to engaging themselves in the new religion; 5 of them reported alcohol use associated with violent behavior; 4 (27%) had prior involvement with other drugs including cocaine and amphetamine; finally, 8 (54%) of the 15 followers had also indulged in heavy cigarette smoking in the past It was further found that there was a total remission of drug use in all 15 hoasca members, along with no deterioration of personality traits or of cognition.

In São Paulo city, there have also been reports on the beneficial effects of hoasca on cases of alcoholism In an MSc thesis, Labigalini (1998) describes the use of hoasca by ex-alcoholics in a religious context; this author and colleagues (Labigalini et al., 1995) consider the ritualized use of hoasca as a therapeutic alternative for alcoholism.

In this respect, it is interesting that β-carbolines are present as endogenous metabolites in mammals, including man (Airaksinen and Kari, 1981a,b; Barker et al., 1981) According to Callaway et al (1994b), 1- methyl-tetrahydro-β-carboline (1-Me-THBC) is formed in the presence of large amounts of acetaldehyde as in cases of alcoholism Whether or not this internal formation of 1-Me-THBC bears some role in the seemingly beneficial effect of hoasca in cases of alcoholic patients should be further investigated.

The hallucinogenic and other toxic effects of hoasca have recently been reviewed (Pomilio et al., 1999; Callaway and Grob, 1998; Ott, 1999).

It has recently been reported that other plants are able to reduce alcohol intake by animals (Carai et al., 2000).

### 3.2. T iboga Baill

The Iboga nation living in Gabon and other nearby West African countries chew the roots of this plant at the religious cult of Bwiti (Bouiti) in order to communicate with their ancestors (Emboden, 1972) Apart from this religious use, eating the roots, according to European explorers in the 19th century, had also stimulant and aphrodisiac effects and greatly increased endurance (Popik et al., 1995) Interest-

ingly enough, ibogaine has more recently been used as a doping agent by athletes (De Sio, 1970) In larger doses, the roots of *T iboga* produce altered states of consciousness that can be considered hallucinations (Emboden, 1972).

Ibogaine was isolated and identified in the beginning of the 20th century (Popik et al., 1995); at least 12 more indol alkaloids have been isolated from the plant (Schultes and Hofmann, 1979; Shulgin and Shulgin, 2001) Ibogaine mimics most of the effects of crude *T iboga* extracts; however, there seem to be some pharmacological differences between both (for a review, see Popik et al., 1995) Depending upon the dosage, ibogaine produces a series of effects Thus, in the initiation ordeal practiced among the African natives, the very large amount of root ingested is enough to provoke a state of lethargy lasting several days; it can also induce convulsions and lethal respiratory arrest (Popik et al., 1995).

In somewhat smaller dosages, ibogaine takes the user to a oneirophrenic state, as observed by Naranjo (1969) in 30 patients: a psychic state similar to a dream, but the person is awake and does not present changes in sensorium, delusions or hallucinations (Popik et al., 1995; Shulgin and Shulgin, 2001) Peripheral signs, such as sudoresis, midriasis, tachycardia, fine tremor and ataxia also occur (Popik et al., 1995) In higher doses, ibogaine is a strong hallucinogenic agent: Hallucinations, illusions, delusions, severe anxiety, etc., are reported by users (Schneider and Sigg, 1957; Shulgin and Shulgin, 2001).

In the mid-1980s, a new era of interest arose for ibogaine, with the filing of a patent for ibogaine treatment of opiate dependence (Sanchez-Ramos and Mash, 1994) Three other patent filings followed in a rapid succession for treatment of cocaine, amphetamine, alcohol and nicotine/tobacco dependence syndromes.

Groups of dependent persons such as the International Coalition of Addict Self-Help (ICASH) and Dutch Addict Self-Help Group (DASH) began to provide treatment with ibogaine and reported that it decreased the craving for opiates and cocaine and their withdrawal symptoms (Mash, 1995) However, further clinical research on ibogaine as an ''addiction interrupter'' was hindered because of the reported deaths of two women who received ibogaine outside the hospital setting Considerable concern was also brought about by the study of O'Hearn and Molliver (1993) showing that ibogaine provoked the degeneration of Purkinje cells of the cerebellum However, the preliminary results of a recent Phase 1 clinical study, carried out with 30 cocaine- or heroine-dependent subjects, demonstrated that single doses of ibogaine (500, 600 or 800 mg) were well tolerated by the subjects, therefore not posing significant safety problems (Mash et al., 2001) The same group also reported (Kovera et al., 2001) that according to preliminary analyses, ibogaine reduces the frequency and the duration of craving episodes and that the patients did not show negative health consequences; quite to the contrary, they reported few to no withdrawal symptoms However, clinical studies on ibogaine effects under controlled conditions are almost nonexistent in the scientific literature Despite the promising results described by Mash (1995) and Mash et al., (2001), further research keeps being hindered by a series of controversies (Morris, 1999).

Fortunately, no such restraints were met in the preclinical research on ibogaine According to the masterly review by Popik et al (1995), ibogaine affects nearly all neurotransmitter systems in the CNS of mammals Thus, not only does it have direct effects on dopaminergic systems, but it also alters the effects of psychotropic drugs on these systems More recent studies have shown that ibogaine is able to interfere with the sensitization of dopamine transmission brought about by repeated exposure of animals to drugs able to induce dependence (Maisonneuve et al., 1997a; Szumlinski et al., 1999a,b, 2000) Ibogaine also attenuates the increase of extracellular dopamine levels induced by nicotine, probably affecting the rewarding effect of nicotine (Maisonneuve et al., 1997b).

According to Popik et al (1995), ibogaine also alters the intracellular calcium regulation in neurons; the voltage-dependent sodium channels; and the serotonergic, opioid, cholinergic, GABA, noradrenergic and glutamatergic systems More recently, it has been reported that ibogaine has a direct effect on glutamate uptake and release (Leal et al., 2001), which could be relevant to explain its neurotoxicity (O'Hearn and Molliver, 1993).

Finally, there are also animal studies showing that ibogaine attenuates the withdrawal symptoms in rats, mice and monkeys (Dzoljic et al., 1988; Aceto et al., 1990; Glick et al., 1992; Popik et al., 1995) and interrupts the cocaine- and morphine-seeking behavior (self-administration) of animals (Glick et al., 1991; Sershen et al., 1994).

## 4. Psycholeptic plants

### *4.1. Analgesic plants*

A recent global review article (Almeida et al., 2001) on plants endowed with analgesic activity disclosed 202 active species involving 79 families; the search encompassed the years 1965–1999, yielding a total of 263 scientific papers, 129 of them published in the 1990s Interestingly enough, *P somniferum* is not present in the list From January 2000 to September 2002, 66 more studies on analgesic plants were published in *Phytomedicine*, *Fitoterapia*, *Planta Medica*, *Journal of Ethnopharmacology* and *Phytotherapy Research*.

The majority of the abovementioned 263 studies were carried out in rats and mice, using extracts obtained from the plants For the evaluation of the analgesic activity, the acetic-acid-induced abdominal writhings were used in 42.1% of the studies, the tail flick response to radiant heat and the formalin test (licking of injected hindpaw) were each used in 18.7% of the studies, and the hot plate test in 17.9%.

There is a large number of chemical compounds present in the hundreds of plants endowed with analgesic properties (Calixto et al., 2000) Thus, there are the phenanthrene group, with or without the gamma-phenyl-*N*-methyl-piperidine moiety present in the alkaloids from *P somniferum*, the cannabinoids from *C sativa*, the salicin and salicylic acid present in *Salix alba* L and other *Salix* spp., and a large number of alkaloids, terpenoids, capsaicinoids, steroids, flavonoids, xanthines, tannins, xanthones, lignans, saponins, lactones, glycosides (Rios et al., 1989; Hua et al., 1997; Calixto et al., 2000).

To the best of our knowledge, only two review articles have been published in the last 5 years on analgesic plants (Calixto et al., 2000; Almeida et al., 2001).

### 4.2. Anxiolytic plants

Anxiety is one of the most common mental disorders affecting mankind Its prevalence is increasing in recent years due to the rather tense "man's zest to win nature" (Dhawan et al., 2001), that is, the rather tense lifestyle imposed on man by the competitive and inhumane atmosphere pervading everyday life.

Anxiolytic substances, mostly belonging to the benzodiazepine group, occupy a prominent post in the ranking of the most utilized drugs by man (Uhlenhuth et al., 1999) to minimize stress, tension and anxiety (Argyropoulos and Nutt, 1999) As a result of these effects, benzodiazepines are also able to treat insomnia (Schneider-Helmert, 1988).

However, the anxiolytic drugs have an unfavorable risk/benefit ratio, as they produce anterograde amnesia, dependence, abstinence syndrome, paradoxical reaction in humans and decay of psychomotor functions (Lader and Morton, 1991; Kan et al., 1997; Schweizer and Rickels, 1998) These symptoms can lead to an increased possibility of car accidents and of fractures (Barbone et al., 1998; Pierfitte et al., 2001).

As at present the etiologic factors responsible for anxiety and tension are not expected to decrease; there is a need for new anxiolytic drugs with less potential to induce adverse reactions.

Since ancient times some plants have been used for such purposes Today, the use of their extracts is gaining increased acceptance by both the medical profession and patients However, for most of the plants, chemical and pharmacological data are incomplete and their active principle(s) have not been identified yet.

Among such plants, *Passiflora incarnata* L., *Valeriana officinalis* L and *P methysticum* deserve special attention.

#### 4.2.1. P incarnata L and other species

*P incarnata* and other species of the same genus (*P alata* Curtis; *P coerulea* L.; *P edulis* Sims.) are widely used in traditional medicine all over European countries and in the Americas for their seemingly sedative and anxiolytic properties (Fellow and Smith, 1938).

*P incarnata* is an official plant in the pharmacopoeias of many countries, such as Great Britain, United States, India, France, Egypt, Germany, Switzerland, etc (Dhawan et al., 2001); *Passiflora alata* is the only species included in the Brazilian Pharmacopoeia (Petry et al., 2001).

Several compounds isolated from *Passiflora* spp have been suggested as the principle(s) responsible for the alleged anxiolytic/sedative effects, such as flavonoids (as apigenin, vitexin, kampferol, homorientin, chrysin), harmane alkaloids (harman, harmalin, harmalol) and pyrone derivatives (malthol), but up to now, the active principles have not yet been identified (Speroni et al., 1996a; Soleimani et al., 1997; Dhawan et al., 2001) It seems, however, that flavonoids are the most likely candidates (Speroni et al., 1996b; Dhawan et al., 2001) In this respect, hydroethanol extracts from *P edulis* and *P alata* were compared as to the flavonoid content and anxiolytic activity (Petry et al., 2001): *P edulis* had near the double concentration of flavonoids and was twice as active when compared with *P alata*.

Soleimani et al (1997) failed to block the anxiolytic and sedative activities of a standardized extract of *P incarnata* by using flumazenil, a known antagonist of benzodiazepine receptors These results suggested that the effects of *P incarnata* are not mediated through an action on the benzodiazepine/GABA receptors.

On the other hand, there is evidence suggesting that the anxiolytic activity of other plants is in some way related to benzodiazepine/GABA receptors (Tihonen et al., 1997) This is the case of *Rubus brasiliensis* Mart., as the anxiolytic activity of its hexane extract is blocked by flumazenil (Nogueira et al., 1998a,b) *Matricaria chamomilla* L and *Matricaria recutita* L seem also to exert an anxiolytic effect, possibly acting on benzodiazepine/GABA receptors through the flavonoid apigenin and GABA itself present in these plants (Avallone et al., 1996; Viola et al., 1995).

#### 4.2.2. V officinalis L.

The name valeriana comes from the latin "valere," meaning a state of being well or happy The plant *V officinalis* was described by Dioscorides as a mild sedative (Morazzoni and Bombardelli, 1995) Other species of the genus *Valeriana* are being used for the same therapeutic purposes, such as *V wallichii* DC., *V fauriei* Briq and *V angustifolia* Turcz.

The crude extract of *V officinalis*, also called valerian, is widely used in many countries: There are at least 25 products containing valerian in the United Kingdom and over 400 in Germany (Houghton, 1999).

From the chemical point of view, two main groups of substances are isolated from *V officinalis* (WHO, 1999): the volatile oil fraction containing bornyl salts, valeranone, valeranal, valerenic acid and other monoterpenes and sesquiterpenoids The simultaneous occurrence of three cyclopentane sesquiterpenoids (valerenic acid, acetoxyvalerenic acid and valeranal) is only present in *V officinalis*, allowing its distinction from other species of the genus.

The second group of substances is represented by valepotriates, of which 90% are represented by valtrate and isovaltrate; they have a common chemical moiety, the furanopyranoid monoterpene skeleton found in the glycosylated forms known as iridoids (Morazzoni and Bombardelli, 1995; Houghton, 1999).

The volatile oil fraction is responsible for only part of the sedative effect; the valepotriates could also not account for all the sedative activity of the plant extract, but they seem, instead, to concentrate most of the anxiolytic activity, as measured in rats and cats (Houghton, 1999).

It has been suggested that different constituents of valerian interact with the GABA system in the brain: Inhibition of GABA-transaminase, interaction with GABA/benzodiazepine receptors and interference in uptake and release of GABA in synaptosomes have been reported (for a review, see Morazzoni and Bombardelli, 1995; Houghton, 1999), which could explain, at least in part, the sedative and anxiolytic effects of *V officinalis*.

Several placebo-controlled, double-blind clinical studies have confirmed the hypnotic/sedative effects of *V officinalis* extracts.Leathwood et al (1982) used an aqueous valerian extract in 128 people and reported a decrease in sleep latency and a significant improvement in sleep quality Leathwood and Chauffard (1985) obtained a significant decrease in sleep latency, measured with the help of actigraphs, in patients suffering from mild insomnia by giving them an aqueous extract of *V officinalis*. Lindahl and Lindwall (1989) observed that a valerian preparation containing primarily sesquiterpenes showed a good and statistically significant effect on poor sleepers Herrera-Arellano et al (2001), using polysomnographic recordings, demonstrated that hydroalcoholic extracts of *V officinalis* and *V edulis* Nutt ex Torr and A Gray containing valepotriates reduced the number of awaking episodes, increased the sleep efficiency index, reduced morning sleepiness and did not affect anterograde memory.

Recently, it has been suggested that valepotriates could be useful in improving the condition of animals (Andreatini and Leite, 1994) and humans (Poyares et al., 2002) during benzodiazepine withdrawal.

#### *4.2.3. P methysticum G Forst (kava-kava)*

The etymological meanings of the words naming this plant are as follows (Singh, 1992): Piper corresponds to pepper, methysticum, from the Greek, means intoxicating drink and kava is equal to bitter or sour The islanders living in Oceania for many centuries have prepared a beverage used in welcoming ceremonies for important visitors Drinking kava seems to induce pleasant mental states such as warm and cheerful feelings, to counteract fatigue and to reduce anxiety, promoting a state of well-being (Pepping, 1999; Billia et al., 2002).

It has been demonstrated that a lipid-soluble extract of the plant retained most of the pharmacological activity in laboratory animals when compared to an aqueous extract (Jamieson et al., 1989) The lipid extracts contain at least seven pyrones, known as kavalactones.

There are several double-blind placebo-controlled studies showing that the kavalactones have a clear anxiolytic effect They improve sleep quality and do not depress mental and motor functions (Münte et al., 1993; Billia et al., 2002) Kavalactones may also be useful for benzodiazepine replacement therapy (Malsch and Kieser, 2001).

Concerning the mechanism of action, the kavalactones reach a rather large number of targets; they interact with dopaminergic, serotonergic, GABAergic and glutamatergic neurotransmissions, seem to inhibit MAO B and exert multiple effects on ion channels (Grunze et al., 2001).

Quite recently, the World Health Organization issued the Alert no 105, warning that kava-containing products were withdrawn from the German market Document QSM/MC/IEA 105, 17 June 2002, states: "Kava-kava and kavaine containing products withdrawn in Germany due to hepatotoxic risks." Further studies on this issue are now in progress (Denham et al., 2002; Blumenthal, 2002) Blumenthal (2002) criticized the previous reports on hepatoxicity, and presented evidence that most of the affected patients already had impaired liver functions On the other hand, Unger et al (2002) recently demonstrated that extracts of kava-kava inhibited the cytochrome $P_{450}$ 3A4 (CYP 3A4), an enzyme that metabolizes a number of important medicaments.

For further readings on kava, see the review articles by Singh (1992), Norton and Ruze (1994), Pepping (1999) and Billia et al (2002).

## 5. Conclusion

1. Plants have been used by human beings since immemorial times to cure diseases and to promote relief from ailments There were times when they were the most important sources of medicines for people However, beginning in the late 1940s, this old form of therapeutics began to lose its importance, being more and more replaced by synthetic remedies The lessons from millennia were forgotten and were considered "unscientific."
2. On the other hand, such ancient use of plants was a lead for scientists in their search for new substances endowed with therapeutic properties It is estimated that nearly 25% of the modern drugs directly or indirectly originated from plants (De Smet, 1997) Several are the examples concerning the CNS: Caffeine, ephedrine, cannabinoids, opioids and reserpine are a few of them However, for the majority of CNS active plants, the active principles are not yet known.
3. The present review shows that Nature provided hundreds of CNS active plants covering the whole spectrum of activity such as psychoanaleptic, psycholeptic and psychodysleptic effects For most of these plants, the

studies are in the initial pharmacological steps, consisting of the administration of crude extracts to laboratory animals Those initial preclinical tests frequently confirm the folk use of the plant However, these results are, in general, far from being sufficient to prove efficacy and safety in human beings (Jonas, 1998; Habs, 1999).

4. The majority of herbal remedies indicated for the treatment of psychiatric ailments are crude or semi-purified extracts, such as *H perforatum*, *G biloba*, *P ginseng*, *Melissa officinalis* L., *V officinalis*, *Crataegus oxyacantha* L., *P incarnata*, *P methysticum*, etc As a rule, authors criticize such approach and suggest that efforts should be directed to obtain the active principle(s) (Wagner, 1993; Bouldin et al., 1999; Habs, 1999; Calixto et al., 2000; Rates, 2001).

Nevertheless, this may not be the ideal path for all cases For example, there has been much discussion on whether cocaine and Δ9-trans-tetrahydrocannabinol are indeed the only substances responsible for the totality of coca and marihuana plant effects, respectively.

The same also applies to caffeine and guaraná A fascinating example of this subject is the Ayahuasca beverage, which shows that in some instances, the biological activity of plants can only be obtained through the simultaneous effects of several substances.

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