Chapter 18

African Psychoactive Plants

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Psychoactive plants have been used by humans for recreational, spiritual, and therapeutic purposes for millennia. Africa possesses an ancient tradition of medicinal plant use and has a rich tradition of using its indigenous plants for these purposes. Given African's high floristic diversity, and the strong connection between plants and the many African cultures and societies, relatively few African psychoactive plants have been investigated in detail when compared to the Americas. This review examines the traditional uses of plants from sub-Saharan Africa that exhibit an effect on the central nervous system. The use, chemistry and pharmacology of well researched and documented plants such as *Catha edulis, Cola* species*, Datura* species, *Pausinystalia yohimbe* (=*Corynanthe yohimbe*) and *Tabernanthe iboga* are reviewed. Newer discoveries are highlighted as well as particular difficulties that are encountered when investigating African psychoactive plants.

Introduction

"Whatever deceives men seems to produce a magical enchantment"
Plato 427-347 BC, Greek Philosopher

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Among the plants used by humans, those able to alter the consciousness and the senses have drawn particular consideration. Frequently surrounded by mystery, superstitions, magical thoughts and religious rituals, they have often been revered and attributed supernatural qualities. This is a phenomenon that can still be observed today, in many tribal shamanistic societies. This is made evident from an African example, Eboka. To quote Schultes and Hofmann's popular book, Plants of the Gods (*1*);

"Zame ye Mebege [the last of the creator gods in Bwiti culture, of Gabon and the Congo] gave us *Eboka* [also known as iboga; *Tabernanthe iboga* root]. One day … he saw … the Pygmy Bitamu, high in an *Atanga* tree, gathering fruit. He made him fall. He died, and Zame brought his spirit to him. Zame cut off the little fingers and the little toes of the cadaver of the pigmy and planted them in various parts of the forest. They grew into the *Eboka* bush (*1*)."

Tabernanthe iboga is used in Bwiti culture to this day to seek information from the 'spirit (ancestral) world', and induces hallucinations accompanied by strong stimulation of the central nervous system (CNS). More recently, anecdotal as well as several scientific reports in Western scientific literature indicate possible anti-addictive effects of *T. iboga* (*2*).

Today, much is known about the chemistry and biological activity of *T. iboga* and a handful of other African psychoactive plants, but the majority of African psychoactive plants have only been investigated superficially or not at all. Until recently most of the research on psychoactive plants has focused on the New World, in particular the Americas (*3*). It is widely accepted that more plants are utilized culturally as hallucinogens (sometimes referred to as entheogens when associated with cultural and religious use) in the New World than the Old (*1*). Of 97 reviewed plants with proven or alleged hallucinogenic potential only eight species are of African origin (*1*). This is contrary to the fact that African traditional cultures and indeed African traditional medicine are the oldest and possible most diverse of all medicinal systems.

Initial explanations for this apparently low occurrence of African psychoactives may be that indigenous Americans retained the fundamental shamanistic characteristics of hunting societies and thus more actively sought mystic visionary experiences by means of hallucinogenic plants than many peoples of the Old World (*4*). However, this may not be the case in Africa, as a large proportion of the population still use and practice traditional 'shamanistic' medicine which often involves 'communication' with ancestral spirits.

A more likely reason suggested by De Smet (*3*) is simply that most of the research, up until recently, on this subject has been conducted in the Americas and Europe. Africa and Australia have largely been neglected. Unfortunately, much of this information may be lost with the erosion of traditional knowledge and the rapid onset of modernization. The introduction of Christianity and Islam to sub-Saharan Africa has also possibly contributed to the loss of traditional knowledge of the psychoactive plants and associated rituals in particular. The uses of plants to induce altered states of consciousness for spiritual and religious purposes were probably not encouraged by these 'newly introduced religions'. In addition, there was a reluctance by many researchers at in the 1980s and 90s

to document and work in areas concerning rituals not of their own beliefs and substances of 'abuse' (*5*).

Psychoactive plants have been used by humans for recreational, spiritual, and therapeutic purposes for millennia (*6*). It is evident from the African plants that have received the most attention, such as *T. iboga* and *Catha edulis* that research has been focused on those plants most commonly used for spiritual or recreational purposes. This is understandable as these plants are often more obvious because of their cultural importance and consequently more noticeable, in particular hallucinogens. The more subtle, often more therapeutically important plants, such as mild stimulants, sedatives, those used to treat convulsions and epilepsy have been sadly overlooked. The CNS-related mode of action of many plants may not immediately be obvious, for example nausea and vomiting are associated with the gastrointestinal system but is often treated via the CNS with scopolamine. The hunger-suppressant (anorectic) activities of South African succulent plants of the species *Hoodia* (7) are another example.

Scope of This Review

Since Louis Lewin's *Phantastica* (*6*) the first comprehensive survey on the use and abuse of mind-altering plants, a large body of information has accumulated on plants that have an effect on the CNS. A thorough treatment of such plants and their active constituents falls outside of the scope of this review they can be found in many recent reviews (*8-11*).

The focus of this paper is to review and identify those psychoactive plant species of sub-Saharan Africa. The biological and cultural diversity of Africa is immense (there are over 2,000 languages represented in sub-Saharan Africa). However, these ancient medicinal systems, usually based on oral traditions, are poorly documented even to this day. In contrast, North Africa and the Middle East have a relatively well documented traditional medicine (*12-14*). The Babylonians, Assyrians and Sumerians recorded herbal remedies in cuneiform on clay tables as long ago as 4000 BC. Not only can we attribute the origins of civilization to North Africa and the Middle East but also possibly the most important psychoactive plant, *Papaver somniferum* (opium poppy), from which the first alkaloid and psychoactive chemical was isolated. Morphine was first isolated by the German pharmacist Sërtuner in 1803 (*15*).

This paper will review some well documented psychotropic genera. Recent studies have shown that members of the Amaryllidaceae, notably *Boophone*, *Crinum* and *Pancratium* have similar alkaloid chemistry to Europeans species. One such alkaloid, galanthamine (named after *Galanthus* the European snowdrop) is currently used to treat the symptoms of Alzheimer's disease (AD) due to its ability to inhibit acetylcholinesterase. The chemistry and biological activity, of the Amaryllidaceae will be discussed in more detail in another review chapter in this book (*16*). Of particular interest, in addition to the potent acetylcholinesterase inhibitors are the Amaryllidaceae alkaloids that bind to the serotonin re-uptake transporter, an important target in recent antidepressant therapy. Recent investigations of *in vivo* and *in vitro* CNS-related biological activity of African medicinal plants are highlighted below. Very few of the

active constituents are known, an area which needs to be tackled in future research if we are to make meaningful progress. This chapter addresses the interface of two very different fields of research, African traditional medicine and neurobiology. Brief introductions to these two fields will be given in the next section to support the discussions that follow.

The Central Nervous System (CNS)

This section reviews basic principles of brain anatomy and function to provide a framework within which to discuss the effect of plants on the CNS. The human nervous system is exceptionally complex, it is the body's major communication system, and is divided into central and peripheral regions. The central nervous system consists of the brain and spinal cord, and the peripheral nervous system consists of all other nerves. Although thought processes and reason are most commonly associated with the CNS, almost every aspect of physiological function is affected by CNS activity. After all, 'Brain death' is widely accepted as the definition of the end of human life (*10*). The follow description of CNS anatomy and physiology can be found in most text books on the and reviews on the subject (*11, 17*).

The spinal cord controls reflex actions, and relays sensory and motor information between the body and the brain, so that the organism can respond appropriately to its environment. The region of the brain where it meets the spinal cord is called the hindbrain (or rhombencephalon), and is composed of the medulla (myelencephalon), pons and cerebellum (metencephalon). The medulla is vital to sustaining life, and controls processes such as breathing, heartbeat and blood flow. The medulla contains receptors for the opioid drugs, such as heroin and morphine, which is why these drugs can cause respiratory depression and death (*11, 17*). The pons is a 'relay station' for signals being carried from the cortex to the cerebellum, which is involved in body movements and coordination, another function affected by opioid drugs.

Above the hindbrain is the midbrain (mesencephalon), which contains two areas that are very important with respect to psychotropic plant use, in particular substance dependence. The ventral tegmental area (VTA) has dopamine rich cell bodies, and projects to the limbic system and forebrain regions (*11, 17*). The VTA is involved in signalling the importance of stimuli that are critical to survival such as those associated with feeding and reproduction. However, many psychoactive drugs also have powerful effects on the VTA, which contributes to the development of dependence by signalling to the brain that psychoactive substances are very important from a motivational perspective. The dopaminergic projection from the VTA to the nucleus accumbens is known as the mesolimbic dopamine system, and is the neurotransmitter system that is most strongly implicated in the dependence-producing potential of psychoactive drugs (*18,19*). Consistent with a relationship among drug sensitization, mesolimbic dopamine, and drug-seeking behavior, alkaloids from the reported anti-addictive *T. ibog a* also blocked the sensitized dopamine responses to morphine and cocaine in the nucleus accumbens (*2*).

Another important midbrain structure is the substantia nigra, which also has dopaminergic projections to the forebrain, but these pathways are involved in coordinating and executing movements of the body. Degeneration of neurons in the substantia nigra leads to the characteristic symptoms of Parkinson disease (*10, 17*).

The forebrain (prosencephalon) is composed of the diencephalon and the telencephalon (cerebral hemispheres). Important areas of the diencephalon are the thalamus, the hypothalamus, and the posterior lobe of the pituitary gland. The hypothalamus is critical for regulating hormonal signals and basic bodily functions – concerning, for example, water balance (osmolarity), metabolism, body temperature and reproductive hormones – as well as responding to changes in these functions (*17*). The hypothalamus also secretes hormones that travel to the nearby posterior lobe of the pituitary gland. A steroidal glycoside with anorectic activity, isolated from the South African plant *Hoodia gordonii* (*20*) increases the content of ATP by 50–150% in hypothalamic neurons (*7*). With evidence of metabolic or nutrient-sensing by the hypothalamus, it is suggested by MacLean and Luo (*7*) that ATP may be the currency of energy sensing, thus changes in ATP levels in the hypothalamus may prompt the appropriate neural, endocrine and appetitive responses. This would be similar to other fundamental hypothalamic homeostatic centers, such as those for temperature and osmolarity (*7*).

The thalamus functions as a relay station for sensory and motor information going to and from the cortex to other areas of the brain and body. The outermost layer of the brain is the cortex, which is made up of layers of nerve cells or neurons, and has a highly folded organization that increases its surface area and the number of neurons that it contains (*11, 17*). The cortex is involved in many aspects of psychotropic plant use, from the primary effects of psychoactive drugs on sensations and perceptions, to the complex behaviours and thoughts involved in drug craving and uncontrolled use (*17*).

Beneath the cortex are several other important structures. The basal ganglia are structures involved in voluntary motor behaviour and consist of the caudate, putamen, globus pallidus and amygdale. The caudate and putamen together are known as the striatum. Degeneration of these structures in some diseases, for example Parkinson's disease, may cause cognitive and motor impairment (*11, 17*).

Neurons and Synapses

Communication in the brain takes place between nerve cells or neurons. Psychoactive substances alter many aspects of communication between neurons, as will be discussed below. Neurons are highly specialized cells that exist in many shapes, sizes and varieties. However, they share the following basic structural regions: cell body or soma, dendrites, axon, and terminal buttons. The cell body, or soma, is the metabolic centre of the neuron, and contains the nucleus and other structures that sustain the neuron. The nucleus plays a role in mature neurons, where it is used to synthesize proteins in response to a wide variety of stimuli (*11, 17*).

Psychoactive substances can affect the expression of DNA, resulting in short-term or long-term changes in neuronal function, and ultimately, behaviour. Dendrites are highly branched processes extending from the cell body of the neuron, which receive chemical messages from other neurons. This branching, and the presence of dendritic spines (small swellings on the surface of a dendrite with which a terminal button from another neuron forms a synapse), allows many different neurons to converge on a single nerve cell, facilitating the coordination and integration of many complex messages. The number of dendritic spines can increase or decrease following exposure to psychoactive substances, thus altering communication between neurons, and most likely contributing to the behavioural and neurological effects of these substances (*11, 17*).

The simplified architecture of a synapse is illustrated in Figure 1. The presynaptic terminal contains vesicles, which are filled with neurotransmitters. Presynapse and postsynapse are separated by a narrow synaptic cleft into which the neurotransmitters are released from the vesicles via exocytosis(*11, 1 7*). Transmitters diffuse across the synaptic cleft and, after a lag period of about 0.5 milliseconds, bind to a receptor on the postsynaptic cell. The ion permeability of the postsynaptic membrane is changed causing a sudden change in the corresponding membrane potential. In neurons within the brain, this electric disturbance can induce an action potential, which will result in a change of mental state.

Many nerves are excitatory, however, the binding of neurotransmitters to inhibitory receptors on the postsynaptic membrane causes the opening of K^+ and Cl^- ion channels that hyperpolarise the membrane and thus blocks the generation of an action potential. Neuroreceptors are found at the post- and presynaptic membrane. Activation of presynaptic receptors usually leads to an inhibition of neurotransmitter release, whereas their inhibition results in an enhanced release of neurotransmitters.

Many types of neurotransmitters have been discovered so far, but in general there are three major broad categories: amino acid neurotransmitters, amino acid-derived neurotransmitters, and peptides (chains of amino acids). The amino acid transmitters include glutamate, GABA, glycine and aspartate (*11, 17*). The monoamines, norepinephrine and dopamine (catecholamines) and serotonin (indoleamine) are derived from amino acids. Large molecule peptide neurotransmitters are generally synthesized in the cell body, and transported along the axons to the synapse. Small molecule neurotransmitters can be synthesized in the terminals. The neurotransmitters will be discussed in more detail later with the plants and plant compounds with which they interact.

There are distinct regions of the brain where cell bodies for a specific neurotransmitter exist, and other regions or ‘projections’ where the axons from those cell bodies project to, and where the neurotransmitter is ultimately released. Thus, not every neurotransmitter is released in every area of the brain compartmentalizing specific regions of the brain to perform specific functions,. s The neurotransmitters and neuroreceptors are the basic elements for signal transduction in the synapses of the central nervous system and are therefore important targets of psychoactive compounds (*17*).

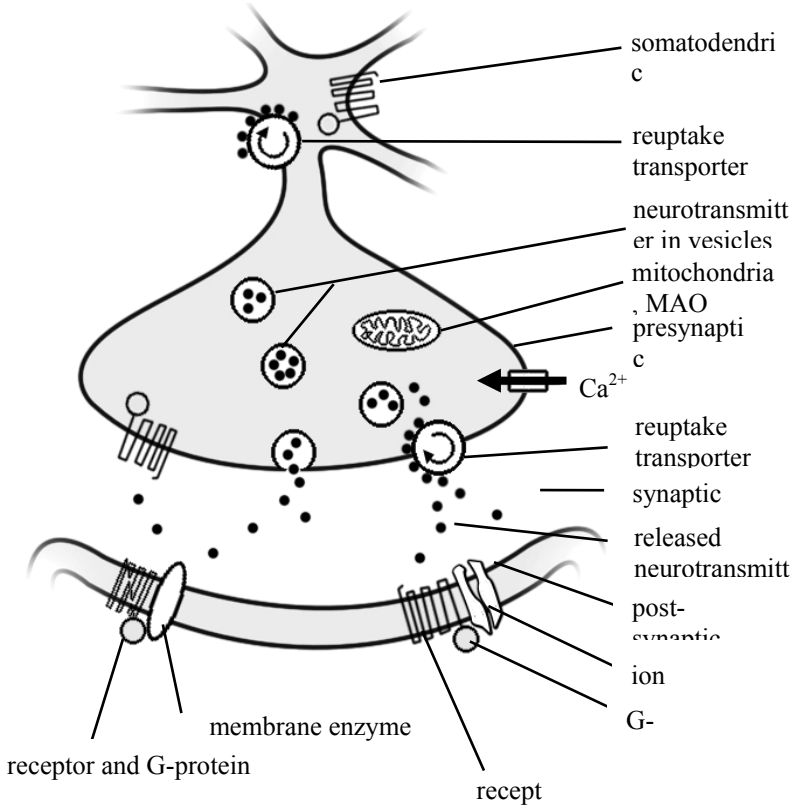


Figure 1. A simplified synapse

Numerous diseases or conditions are a result of this chemical neurotransmission process malfunctioning. The CNS is complex in both structure and function, making it particularly vulnerable to factors causing it to malfunction. This important and complex system within animals represents an important target area which is ideal for interference by defense chemicals. Indeed, many secondary metabolites in both plants and animals are known to effect neurotransmission and signal transduction (*11, 17*) . Traditional medicine and many modern pharmaceuticals utilize these properties in an attempt to treat ailments of the CNS.

Psychoactive plants of African origin

African views of illness and treatment

Culture is the lens and guide we use in constructing, defining, and interpreting the world around us. Thus, people from different cultural contexts and traditions define and experience events (i.e. illness) in different ways. This

is particularly true of views about mental disorders and subsequently their diagnosis and treatment since these cannot be separated from cultural experiences. To determine which plants used in African traditional medicine may act on the CNS, an understanding of indigenous or traditional African views of illness and treatments are required. A brief interpretation follows, however more thorough treatments on African culture as a whole and specific regions are available (*21-32*).

In many traditional cultures, illness is believed to be caused by psychological conflicts or disturbed social relationships that upset an equilibrium which is expressed in the form of physical or mental problems (*33*). Although Africa has a diverse culture, there is a common thread that follows that the disruption of this equilibrium, what we call illness, may be caused by external psychological or spiritual factors, or both, that relate to African cosmology and "threaten the intactness of the person" (*34*). In traditional cultures, then, healing involves restoring this equilibrium.

In general, many African cultures group illnesses into three categories (*32*). Illnesses which have no discernible moral or social cause; these tend to be minor ailments such as rashes and colds. This is the only class of illness that occurs by chance, and for which causes are not sought (*30*). Some illnesses are considered 'modern diseases' which can be contracted by people anywhere in the world, and which are believed to be first introduced into Africa by European settlers (*27*). Lastly, there is the belief that there are diseases which only African people can contract, and to which all African people are vulnerable (*23*). A large majority of mental disorders fall under this last category. The 'epidemic' of *indiki* spirit possession in Zululand, South Africa from the 1890s to 1914 is an interesting example (*35*).

More importantly, African cultures define two types of causes for illnesses (*21,32*). Firstly, a proximate cause, which accounts for how a disease is contracted (*30*). Infection and contagion from pollutants are examples of proximate causes (*26*). Secondly, an ultimate cause, which accounts for why a disease is contracted by a particular person. A simple explanation by Green (*27*) clarifies, 'a mother may recognize that her infant has diarrhea because flies settled on and contaminating its food (proximate cause), but she will also want to establish who sent the flies to harm her child (ultimate cause)'. The material types of treatment (i.e. herbal remedies) are often considered of secondary importance and only complementary. The primary concern of African traditional healing is to discover who, or what has caused the imbalance or illness (i.e. the ultimate cause).

Three main types of ultimate cause are often raised in explaining illness, contact with pollutants (literal and/or spiritual), sorcery and ancestral punishment. Pollutants are considered to often originate in other people's bodies, and include semen, menstrual discharge, vaginal secretions, and blood (*26*). Death is also believed to be a pollutant (*23*). Since contact with pollutants cannot always be avoided, people fortify themselves from contamination by maintaining strict moral codes and observing protective rituals (*27*). Illness is often suspected to be inflicted by people who have been offended by a victim's behavior. Failure to honor filial obligations, violence, or other forms of uncooperative behavior risk creating a level of offence which elicits kin or

neighbors to seek redress through 'witchcraft' (*36*). The 'survival' of ancestors in the spirit world depends on them being accorded regular attention from living offspring (e.g. respect paid to *mizimu* in Uganda and *amadlozi* in South Africa). This attention is manifest in rituals, sacrifices, avoidance of taboos, and high standards of social behavior. Where these requirements are not met, illnesses can be sent as a warning or punishment (*23*).

Both proximate and ultimate causes require treatment if a disease is to be cured. Diseases manifest themselves not only in physical symptoms, such as fever or pain, but in mystical disturbances of the blood commonly described in terms of 'impurities' or 'heat' (26). To treat proximate causes and physical symptoms, people may consult medical personnel and/or traditional healers for appropriate remedies. However, treatment for ultimate causes must also be sought, and since these lie within the mystical or spiritual domain, it is believed that only traditional healers or diviners are capable of useful insights and therapies (*37*).

These cultural beliefs make it difficult for outsiders to understand and determine the use, in western terms, of many African medicinal plants. Literature on African medicinal plants is replete with references to plants used to counteract curses and appease the ancestors. For example the plant *Asparagus virgatus* (= *Protasparagus*) is known by the Zulu people of South Africa as '*iphinganhloya*' which means 'what suppresses the ill-omen or curse' (*38*). Many of these plants are not ingested but are usually carried about on the person in the form of a protective amulet or charm (referred to as '*imfingo*' Zulu culture**)** or administered by sprinkling onto the person or around the homestead (referred to collectively as '*intelezi*' Zulu culture). These are assumed to have no physiological effect on the patient, but perhaps provide some 'psychosomatic' protection to the person. Some remedies such as those referred to as '*amakhubalo*' in isiZulu which are plant materials, that are ingested, for protection from 'evil' and thus, may have a physiological effect on the user. It is therefore not only important to know the symptoms, including the proximate and ultimate causes, but also the method of administration of the plant material, many of which are often neglected in ethnobotanical literature.

A closer look at plants used in African traditional medicine reveals a large number of plants with potential psychoactive properties. One study in South Africa list 306 plants from 94 families with reported psychoactive uses in southern Africa (*39*). Thirty plants belonging to 21 families and traditionally used in southern Nigeria by herbalists for the management of mental disorders (including amnesia, insomnia and senile dementia) have been reported (*40*). Neuwinger (*41*) cites more than 1 750 potential psychoactive traditional African medicinal applications (**Figure 2**); the majority of treatments were aphrodisiacs and sexual stimulants. What is also of interest is the large number of treatments with potential CNS suppressant effects, for example 300 plants for treating epilepsy and convulsions alone. In addition to these there are plants to calm the insane, to treat insomnia, hysteria and tranquilizers (*41*).

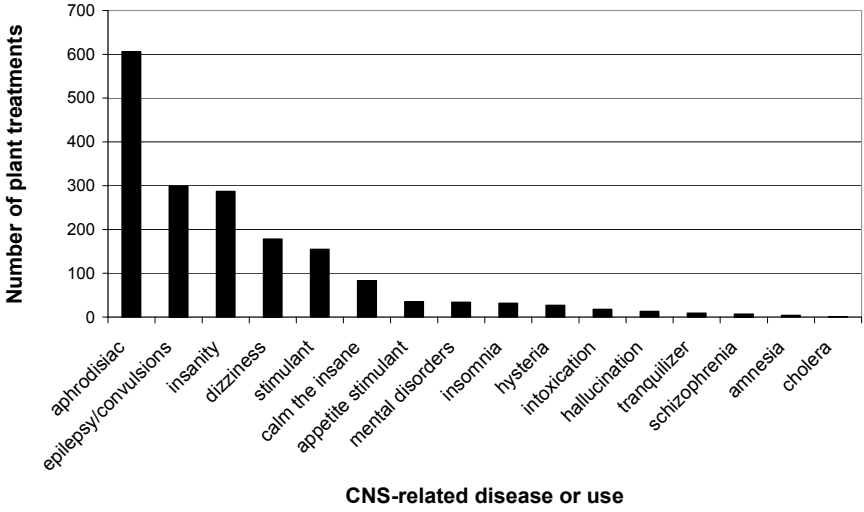


Figure 2. African traditional plant treatments with potential psychoactive properties based on their traditional uses reported in Neuwinger (41).

There are surprisingly few traditional African treatments for memory loss (amnesia), to improve cognition or treat age-related neurodegenerative diseases like Alzheimer's and Parkinson's disease. Four species are reported to be used in southern Nigeria by herbalists for amnesia (*40*). These include *Boerhaavia diffusa* (Nyctaginaceae), the roots of which are reported to contain liriodendrin (lignan) a Ca^{2+} channel blocker (*42*). Decoctions of male inflorescences of *Carica papaya* (Caricaceae) with *Zingiber officinale* (Zingiberaceae) and *Pauridiantha viridiflora* (Rubiaceae) are also used to treat amnesia. *C. papaya* contains (*S*)-(-)-cotinine (pyridine pyrrolidinone) a major brain metabolite of nicotine and acetylcholine receptor agonist (IC_{50} = 30 μM) (*42*).

Plants and compounds with anticonvulsant, anxiolytic and sedative activity

Substances that slow or reduce brain activity, notably by a reduction in neuronal activity, are often referred to as CNS depressants. Central nervous system depressants are routinely used to treat anxiety, epilepsy and insomnia. They are also important in general anesthesia for major surgical operations.

Epilepsy is a symptom complex consisting of repeated unprovoked seizures. Seizures are classified according to the area of the brain in which the seizure originates; partial seizures and generalized seizures (*43*). During seizures some of the patients will experience convulsions. There are numerous causes for epilepsy (*43*). The link between abnormal electrical activity, as detected by electroencephalograph (EEG) and levels of chemical substance (such as neurotransmitters) is still relatively unexplored. However, abnormal activity of electrical impulses is often associated with epilepsy. Therapeutic use of antiepileptic drugs has focused on lowering Na^{+}, K^{+}, or Ca^{2+} flux in neurons,

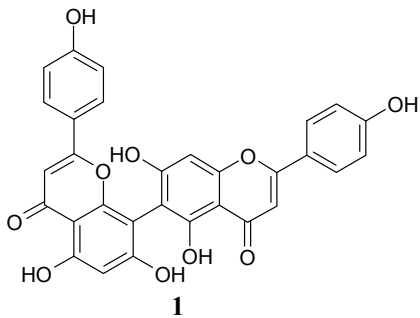
inhibiting glutamate neurotransmission, or promoting γ-aminobutyric acid (GABA) activity at Cl^- channels.

In many traditional Africa societies epilepsy in particular is thought to be due to possession by evil spirits (*44*), and is seen traditionally as a highly contagious (a pollutant) and shameful disease. It has severe social implications in African communities as it carries a stigma and sufferers are often shunned and discriminated against with respect to education, employment and marriage (*45-50*).

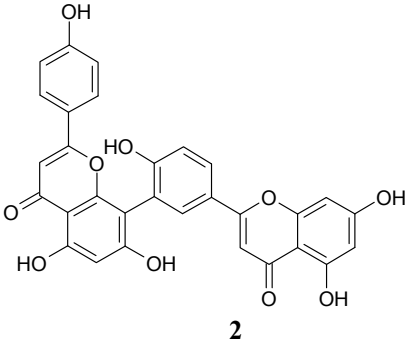
Overexcitement of the central nervous system, commonly results in mania, a collective term for symptoms that include frenzied or hyperactivity, lack of concentration, and irrational thoughts and behavior. Anxiety is also associated with overexcitement of the CNS, which greatly effects ones ability to function normally. The neurobiology and control of anxious states has been extensive reviewed (*51*).

A common group of anticonvulsant, anxiolytic and sedative agents are the benzodiazepines, which bind to the $GABA_A$-benzodiazepine receptor complex where they enhance the affinity for the inhibitory neurotransmitter GABA. A GABA stimulus on the $GABA_A$-receptor causes an influx of chloride ions into the cell. This influx causes hyperpolarization of the membrane, making it more difficult to generate action potential (*52*). As a result the neuronal impulse is inhibited, the CNS is suppressed and an anticonvulsant activity is achieved.

In an initial screening of southern African medicinal plants for compounds with an affinity for the $GABA_A$ receptor benzodiazepine site several *Rhus* species showed interesting activity (*53*). It was later discovered that this activity was largely due to two biflavonoids (*54*). Agathisflavone [**1**] and amentoflavone [**2**] competitively inhibited the binding of ^{3}H-Ro 15-1788 (flumazenil) with a *K*i of 28 and 37 nM, respectively. Extracts of *Rhus dentata* and *R. pentheri* were not as active as the extract from *R. pyroides*, this was found to be due the presence of amentoflavone only in *R. pyroides*, and the content of agathisflavone was higher in *R. pyroides* than in *R. dentate* and *R. pentheri*. Amentoflavone [**2**] is found in a number of plants with CNS-related properties, including ginkgo (*Ginkgo biloba)* and St. Johns Wort (*Hypericum perforatum)* (*55*). The monomer apigenin, which was detected in *Rhus dentata*, only had a *K*i value of 7.6 μM. Thus, the biflavones are far more active than the monomer. Apigenin has also been detected in the flowers of chamomile, the popular herb *Matricaria recutita* (Asteraceae) (*56*).



1
Agathisflavone



2
Amentoflavone

The discovery of chrysin (5,7-dihydroxyflavone), and several other flavonoids shown to possess activity through interaction with the benzodiazepine receptor (K_i = 4 μM) (*57*), started the search for similar natural anxiolytics. Several flavonoids have been found to possess partial allosteric modulatory action at the $GABA_A$ receptor complex, and can potentially play a role in the modulation of anxiety. These flavonoids therefore constitute a promising class of naturally occurring compounds for the treatment of anxiety. These naturally occurring flavonoids often bind to the benzodiazepine receptor with only moderate affinities. Through synthesis of chemical libraries and molecular modeling of the flavonoid binding to the benzodiazepine receptor pharmacophore, several research groups have been able to develop synthetic derivatives with higher affinities for the benzodiazepine receptor (*58,59*).

Several southern African plants have shown *in vivo* anticonvulsant activity against seizures produced in mice by pentylenetetrazole, picrotoxin, bicuculline and *N*-methyl-DL-aspartic acid. However, the active constituents are yet to be identified. The plants include *Leonotis leonurus* (Lamiaceae) (*60*) which is reported to have narcotic effects and is used as a substitute for *Cannabis sativa* (*61*). The aqueous extracts of *L. leonurus* (400 mg/kg) protected against or delayed seizures induced by pentylenetetrazole, picrotoxin and *N*-methyl-dl-aspartic acid, but did not protect against bicuculline-induced seizures. In a later study, the ethanol extracts of the three species of *Leonotis* had weak $GABA_A$-benzodiazepine receptor binding activity only at the highest concentration tested (10 mg/ml) (*53*) but the aqueous extracts were not active, suggesting that the anticonvulsant mechanism is not via $GABA_A$-benzodiazepine receptor.

Watt (*62*), one of the earlier researchers to recognize the potential of African plants in improving mental health, reported the use of *Cotyledon orbiculata* (Crassulaceae) leaves to treat epilepsy. Again, *in vivo* studies have demonstrated both aqueous and methanol extracts of *C. orbiculata* have anticonvulsant properties (moderate protection against pentylenetetrazole, bicuculline, picrotoxin and *N*-methyl-dl-aspartic induced seizures in mice) (*63*). However, the ethanolic extract did not show *in vitro* $GABA_A$-benzodiazepine receptor binding activity (*64*).

Another study investigated a Northern Sotho remedy, *Sehlare sa Seebana*, for treatment of epilepsy. The recipe for this herbal remedy contains six plants, *Acrotome inflata*, *Aptosimum indivisum*, *Asparagus suaveolens*, *Barleria bolusii*, *Commiphora marlothii* and *Sesamum triphyllum*. Equal parts of the plants are placed in a red-hot clay pot and the patient inhales the smoke (*65*). Both aqueous and ethanol extracts of *Aptosimum indivisum* and *Asparagus suaveolens* and the aqueous extract of *Commiphora marl othii* showed good dose-dependent $GABA_A$-benzodiazepine receptor binding. Most of the plants have not been chemically investigated. Three metabolites: verbascoside, pinocembrinin 7-neohesperidoside and shanzhiside methyl ester were isolated from *A. indivisum*. *B. bolusii* contains verbascoside, which is known to inhibit the GABA receptor, but did not show much activity (*65,66*).

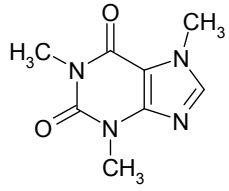
Although a large number of plants are used traditionally all over the world for the treatment of epilepsy and convulsions, there is still no substantial use of herbal products or constituents in western medicine that have been shown to be both efficacious and safe for this condition (*10*).

Plants and associated compounds which stimulate the CNS

The concept of using plants to help one stay focused and alert for long periods has a strong appeal. Stimulants are amoung the earliest psychoactive plants used by humans and are the most widely used psychoactive throughout the world today. There are strong cultural and social links with stimulant use and consequently, these plants have spread around the globe with the movement of people. Africa has adopted many customs of stimulant use from the numerous cultures that have settled on the continent. Betel chewing is one such practice, originating in southeast Asia where an estimated 200-400 million people are reported to use it (67). Betel is composed of the fruit or nut of the areca palm (*Areca catechu,* Arecaceae), the leaf of the betel pepper (*Piper betle*), and lime (calcium hydroxide). These plants can now be found through-out Africa. It is Africa that has made the largest contribution to stimulant use, coffee. The coffee plant, *Coffea arabica* originates from the highlands of south-west Ethiopia. The beverage consumed world-wide is produced from the seeds of mostly *C. arabica* but may contain other varieties (e.g. *C. canephora, C. liberica*).

Cola spp. (Sterculiaceae)

Caffeine [**3**] is possibly the most widely used psychoactive substance in the world. Caffeine is valued because of its stimulant-like behavioural activity on mood and performance. Caffeine is found in several plants which are widely known and employed throughout the world. Wherever these 'caffeine containing plants' were found, indigenous groups have recorded their mildly stimulant effects and have grown habituated to their use. The most well-known sources in contemporary western society are coffee, tea, caffeinated soft drinks, cocoa, chocolate and certain medications.



3
Caffeine

More traditional sources include *Ilex* and *Paullinia* species valued by the indigenous people of South American, whereas *Cola* spp. are an important social drug for West African peoples (*68*). Kola nuts have also played an important role in western Africa as a valuable commodity. The Yoruba farmers of western Nigeria recognize at least four kinds of kola nuts, which probably belong to three different *Cola* species (*C. acuminata*, *C. nitida* and *C. verticillata*) (*3*).

The main mechanism of action of caffeine is the antagonism of adenosine receptors (*69-71*). Adenosine decreases the firing rate of neurones and exerts an inhibitory effect on synaptic transmission and on the release of most

neurotransmitters, while caffeine increases the turnover of many neurotransmitters, including monoamines and acetylcholine (*70*).

Catha edulis (Celastraceae)

Khat, *Catha edulis,* is known throughout Africa by many names, e.g. qat in Yemen; in Kenya it is known as miraa; South Africa the bushman's tea, igqwaka (Xhosa) and inandinandi (Ndebele). The Shona of Zimbabwe call it mutsvahari. The spelling khat has been chosen here because it is the most widely used one in the literature but can also spelled qat, kat, cat, ghat or tchat.

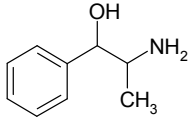
Figure 3. Catha edulis (khat), the two youngest leaves from fresh shoot tips are chewed in East Africa, the Middle East, including Ethiopia, Tanzania and North Yemen

The principal cultivation and production areas of *C. edulis* are in Ethiopia, particularly in Harar district, and in Yemen (*72*). It is also cultivated, to a lesser extent, on the slopes of Mount Kenya and grows wild in many mountainous parts of eastern Africa including South Africa, Uganda, Tanzania, Rwanda and Zimbabwe (*72,73*). The most debated historical issue about khat is whether it originated in Yemen and then spread to Ethiopia (*74*), or *vice versa* (*75*).

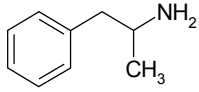
The psychotropic properties and use of *C. edulis* have been known for centuries in East Africa, the Middle East, including Ethiopia, Tanzania and North Yemen (*8*). The medicinal properties of khat for the treatment of depressive states, as an anorectic and stimulant are reported as early as 1237 by the Arabian physician Naguib Ad Din (*76*). However, khat use has largely lost its therapeutic aspects becoming a popular habit among several million people who consume khat daily because of its euphorigenic and pleasurable effects. Khat is reported to induce a clear anorectic effect (*77*), together with euphoria,

excitation and cheerful sensation (*78,79*). Among certain populations, particularly in Yemen, khat is mainly used in a social setting, and consumption of the drug has become part of the cultural tradition. The habit is socially sanctioned and even considered prestigious, with many houses having a special room devoted to khat chewing. The usual method of ingestion is chewing of the young leaves. Recently, use of this plant has reached other parts of the world (*80*). In southern Africa infusions of the leaves are used to treat coughs, asthma and other respiratory ailments (*61*).

These effects are produced mostly by phenylpropanolamines present in the leaves. These include cathinone [**4**] (*S*-α-aminopropiophenone), cathine [**5**] [(-)-1S, 2S-norpseudoephedrine] and (-) -1R, 2S-norephedrine (*8*). These substances have pharmacological properties similar to those of amphetamine [**6**] (*81*), as they induce the release and inhibit the uptake of dopamine and norepinephrine in CNS (*82*). In addition to the known phenylpropylamines, the presence of other amines such as merucathine, pseudomerucathine and merucathinone have been identified (*83, 84*). Cathinone, being a ketoamine base, is extremely unstable and, in particular, it can be transformed into (+)-norpseudoephedrine and (-)-norephedrine by an enzymatic reduction. It can also be oxidized to give 1-phenyl-1,2-propandione, while the cathinone dimers, such as 3,6-dimethyl-2,5-diphenylpyrazine are purely artifacts of the isolation (*85*).



4
Cathinone



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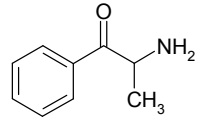
Cathine



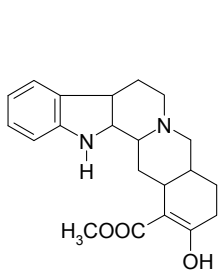
6
Amphetamine

Hartogiella sc hinoides (Celastraceae) leaves are reported to have similar stimulant activity to *C. edulis* when chewed (*86*). Leaves are chewed in southern Africa to relieve thirst, prevent fatigue and are reported to cause weight loss due to lack of appetite (*61*). Other members of the Celastraceae with psychoactive uses are *Maytenus sene galensis* and *M. hetero phylla* which are used to treat epilepsy in Zimbabwe and East Africa respectively (*87,88*), however little is know about their chemistry.

Pausinystalia yohimbe (Rubiaceae)

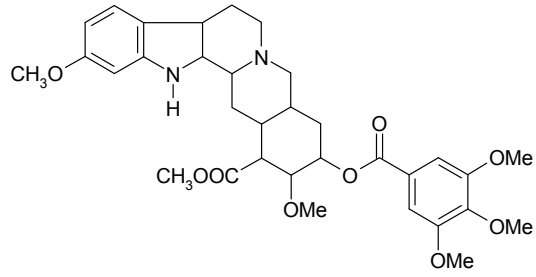
The stem bark of *P. y ohimbe* (= *P. j ohimbe; C orynanthe yo himbe*), '*yohimbe'* as it is known in Cameroon, Gabon and Congo is used traditionally as an aphrodisiac and stimulant to prevent sleep (*41*). The bark contains 1-6% of indole alkaloids, most of which are yohimbane-type alkaloids, the main one being yohimbine [**7**], which is structurally related to reserpine [**8**] (*89*). Yohimbine is a selective inhibitor of α-2- adrenergic receptors and, while at low dose it has hypertensive activity, at high dose it is hypotensive (vasodilation of peripheral vessels). It is the vasodilation of peripheral vessels, and especially vasodilation of the corpus cavernosum, which is the cause of the reputation of yohimbine as an aphrodisiac (*90*). Tests have shown, indeed, that increased

libido and easier ejaculation result from treatment with yohimbine. It is used with success in the treatment of erectile dysfunction (*90*). However, it is not sufficiently free from serious adverse effects (such as tremors, sleeplessness, high blood pressure and rapid heartbeat) and drug interactions, which warrant some form of prescription control (*91*).



7

Yohimbine

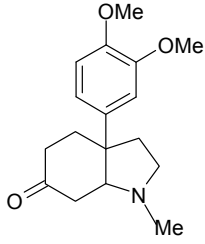


8

Reserpine

Sceletium tortuosum. (Mesembryanthemaceae)

The mood elevating properties of *Sceletium tortuosum* have been attributed to mesembrine [**9**], an alkaloid with potent selective serotonin (5-HT) re-uptake inhibition activity (*86*). Other sceletium alkaloids as they are now referred to are mesembrenone, mesembrenol and tortuosamine. The use of mesembrine-type alkaloids was patented (*92*). Selective serotonin (5-HT) re-uptake inhibitors (SSRIs), like mesembrine, have become important treatments in the therapeutic management of depression (*93*). Several southern African medicinal plants, in particular Amaryllidaceae, have shown *in vitro* affinity for serotonin re-uptake transporters (*94,95*). Several active alkaloids have been identified from *Boophone* and *Crinum* species (*95, 96*).



9

Mesembrine

Narcotic and hallucinogenic plants and their active constituents

Narcotic plants are used primarily to induce sleep and are used to treat insomnia and in anaesthesia (*10*). In South Africa the Zulu use the powder bark of *Tecomaria capensis* (Bignoniaceae) to make infusions that are said to induce sleep (*39*). There are many examples of plants used for similar purposes,

however, no research has been done to validate these. The pharmacology and chemistry of *Boophone disticha*, the bulb infusions of which are used to induce hallucinations for divinatory purposes, are well documented (*16*). Alkaloids isolated from *B. disticha* bulbs include buphanamine, buphanidrine, buphanine buphanisine, haemanthamine, nerbowdine, undulatine, lycorine, crinamidine, crinine, 3-*O*-acetylnerbowdine, ambelline, buphacetine and distchamine (*95,97*). Much of this research was stimulated by the toxic nature of this plant and the numerous poisonings and deaths that have resulted from its use.

Datura sp. (Solanaceae)

Datura stramonium, a naturalized toxic weed that is probably indigenous to tropical America but now widely distributed throughout the world including sub-Sahara Africa. The seeds are the most potent part of the plants, followed by the roots, stems, leaves, and flowers, and as few as ten seeds are sufficient for psychoactivity.

Atropine and scopolamine are found in jimson weed (*Datura stramonium*), nightshade (*Atropa belladonna*) and mandrake (*Mandragora officionarum*), and scopolamine alone is found in henbane (*Hyoscyamus niger*) (*98*), all of which are popularly grown as ornamental flowers. Dissociative rather than entirely hallucinogenic, both chemicals act as CNS depressants and competitively antagonize muscarinic cholinergic receptors. These two chemicals have considerable application in ophthalmology to dilate pupils (atropine), anaesthesia to decrease secretions and treat bradycardia, toxicology to treat organophosphate and nerve gas poisoning, and in emergency medicine for cardiac arrest (*99*).

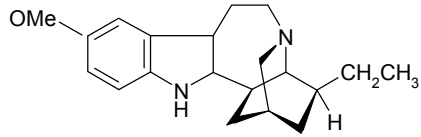
Scopolamine is also used as a treatment for motion sickness. In excess, these plants can cause a toxic delirium that may lasts hours to days, marked by amnesia, confusion, dissociation, hallucinations, delusions, euphoria, and sometimes episodes of bizarre self-injury (*100*).

The delirium caused by *Datura* is evident by the Afrikaans name, *malpitte* which translates as ‘mad seeds’ (*86*) and its Zulu name *iloyi* which is possibly derived from *–loya* which means to bewitch, or cast a spell on. In tropical West Africa, *Datura* spp. are used in native beer or in palm wine to add a stupefying or narcotic effect. A drink made from the seeds of *D. metel* is given as an intoxicant to Fulani youth to incite them in the ‘Sharo contest’ or ordeal of manhood (*101*).

Tabernanthe iboga (Apocynaceae)

The Iboga people (Bwiti and Mbiri cults) living in Gabon and other nearby West African countries chew the roots of this plant in order to communicate with their ancestors (*1,2*). It is also used as a stimulant to keep hunters awake and motionless while stalking prey (*2*). European explorers in the 19th century, eating the roots had also stimulant and aphrodisiac effects and greatly increased endurance (*102*). Ibogaine [**10**] was isolated and identified in the beginning of

the 20th century (*102*) and at least 12 more related indole alkaloids have been isolated from the roots of *T. iboga* (**Table 1**) (*42*). Ibogaine, at low doses has primarily a stimulant effect, increasing alertness and reducing fatigue, hunger, and thirst (*103*). Pharmacological differences between Ibogaine and crude *T. iboga* extracts are slight, suggesting that the other indole alkaloids may play a role in the psychoactivity observed (for a review, see *102*)



10
Ibogaine

Until the mid-1980s ibogaine had no apparent therapeutic value. Interest was stimulated with the filing of a patent for ibogaine treatment of opiate dependence. Four other patent filings followed in rapid succession for treatment of cocaine, amphetamine, alcohol and nicotine/ tobacco dependence syndromes (*8,2*). Current research has focused on 18-methoxycoronaridine, a synthetic derivative of ibogaine (*104-106*).

Ibogaine is only one representative of a class of complex indole alkaloids that are particularly abundant in the Apocynaceae family, and it is likely that other naturally occurring alkaloids with related structures will also exhibit interesting CNS activity. *Tabernaemontana* and *Voacanga* species are known to possess a similar chemistry to *Tabernathe* species (*42*). There is evidence that certain *Voacanga* species are used as stimulants in Africa (*107*). *V. africana* is used in Cote d'Ivoire to treat convulsions in children and madness (*108*). The stem bark of *V. bracteata* has a 2.46 % alkaloid content (*109*), although these alkaloids are chemically related to ibogaine, there is no evidence that they are psychoactive. Voacangine is also present in *Tabernaemontana coffeoides*, which is used as a stimulant in Madagascar (*107*).

Table 1. Biological activity of Tabernanthe alkaloids (adapted from Polya (42)

Compound	Biological activity
Tabernanthine (= 13-Methoxy-ibogamine)	Benzodiazepine receptor agonist (flunitrazepam displacement (IC_{50} = 150 μM), NMDA-Glutamate-receptor antagonist (K_i = 11 μM), σ1-receptor ligand (IC_{50} = ~1 μM) and σ2-receptor ligand (IC_{50} = 0.2 μM), Opiate (κO)-receptor ligand (K_i = 0.2 μM), μO-receptor (IC_{50} >100 μM ;), δO-receptor (K_i = 3 μM),
(±)-Coronaridine (= Carbomethoxy-ibogamine)	NMDA-Glutamate-receptor antagonist (K_i = 6 μM), Opiate (μO)-receptor (K_i = 3 μM), δO-receptor ligand (K_i = 8 μM), κO-receptor ligand (K_i = 4 μM), Voltage-gated Na^+ channel antagonist (K_i = 16 μM) cytotoxic, diuretic and oestrogenic
Ibogaine (=12-Methoxy-ibogamine)	$5HT_3$-receptor ligand (IC_{50} = 4 μM), Dopamine and 5HT re-uptake transporter inhibitor (IC_{50} = 4 and 0.6 μM respectively), Dopamine receptor (D1) ligand (IC_{50} > 10 μM), Dopamine receptor (D2) ligand (IC_{50} > 10 μM), NMDA-Glutamate-receptor antagonist (K_i = 1 μM), σ1-receptor ligand (IC_{50} = 9 μM) and σ2 receptor ligand (IC_{50} = 0.2 μM), Opiate (κO)-receptor ligand (IC_{50} = 25 μM ; K_i = 2 μM), μO-receptor (K_i = 4 μM), δO-receptor (K_i > 100 μM), Adenosine-receptor (subtype A_1) ligand, Muscarinic acetylcholine-receptor ligand, α1-Adrenergic-receptor (IC_{50} = 7 μM), Voltage-gated Na^+ channel antagonist (K_i = 9 μM), Anticonvulsant, hallucinogen, inhibits morphine dependence, anti-addictive, increases synaptic 5HT)
Noribogaine (=12-Hydroxy-ibogamine) Metabolite of Ibogaine	Dopamine receptor (D1) ligand (IC_{50} > 10 μM), Dopamine receptor (D2) ligand (IC_{50} > 10 μM), Opiate (κO)-receptor ligand (K_i = 4 μM), μO-receptor (K_i = 0.2 μM),
Ibogamine	NMDA-Glutamate-receptor antagonist (K_i = 6 μM), σ1-receptor ligand (IC_{50} = ~1 μM) and σ2 receptor ligand (IC_{50} = 0.1 μM), Opiate (κO)-receptor ligand (K_i = 3 μM), μO-receptor (K_i > 100 μM), δO-receptor (K_i > 100 μM), Voltage-gated Na^+ channel antagonist (K_i = 8 μM), Brachycardiac activity, cytotoxic and hypotensive
Tubotaiwine	Adenosine-receptor (subtype A_1) ligand. Opiate-receptor ligand (K_i = 2 μM) Analgesic (mouse abdominal relaxant)

Members of the Apocynaceae worthy of further investigation are *Acokanthera op positifolia* which is administered to treat convulsions and fits

(*110*). *Acokanthera* species are well documented as arrow poisons (cardiac glycosides), and are used extensively in Africa (*111*). Another source of poisonous cardiac glycosides for arrows are *Strophanthus* species. Some species (possibley *Strophanthus gerradii* and *S. petersianus*) known to the Zulu of South Africa as '*ubuhlungubendlovu*' or 'pain of the elephant' are reported to be used to treat hysteria (*112*), however no details are given as to how the plant is administered. Both *Acokanthera* and *Strophanthus* are also used as ordeal poisons in East Africa (*113*).

Conclusions

The African flora is indeed rich in psychoactive substances. There is clear evidence from ethnobotanical surveys and screening programs for CNS-related activity to support this. Africa's indigenous people have in the past and to a large extent continue to utilized these plants for cultural, medicinal and recreational purposes. As is the case in many areas concerning African traditional medicine, there is still much research required, to determine the active constituents, their mode of action and safety. Due to the supernatural properties attached to these plants by many African cultures it is often more difficult to identify psychoactive plants based on their traditional uses. The ethnobotany of many African cultural groups is poorly documented, and requires urgent detailed research before this valuable knowledge is lost. A better understanding of the indigenous or traditional interpretations of mental illness and treatments, especially on the use, preparation and administration of these plants, will help in deciphering the science behind their utilization and will potentally provide new candidates for the development of modern drugs

The chemistry and pharmacology of most African psychoactive plants are unknown. The safety and validation of these plants continues to be assessed with promising outcomes. There remains many opportunities where advances in this field could provide a better understanding of African traditional medicine and the mode of action of these phytochemicals.

Acknowledgements

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