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THE POSSIBLE ROLE OF AMAZONIAN PSYCHOACTIVE PLANTS IN THE CHEMOTHERAPY OF PARASITIC WORMS — A HYPOTHESIS*

ELOY RODRIGUEZ and JAN CLYMER CAVIN

Phytochemical Laboratory, Departments of Ecology and Evolutionary Biology and Developmental and Cell Biology, University of California, Irvine, CA 92717 (U.S.A.)

JAN E. WEST

Department of Botany and Plant Sciences, University of California, Riverside, CA 92521 (U.S.A.)

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Summary

Data from the pharmacological and ethnobotanical literature are presented to support the hypothesis that tropical hallucinogenic plants (which contain indole or isoquinoline alkaloids) were selected by Amazonian people for their antiparasitic properties and were probably incorporated into religious ceremonies.

Introduction

Over the last half century investigations by ethnobotanists have shown that the use of hallucinogenic drug plants by indigenous peoples of tropical America has a long history and is an integral part of their culture. During native ceremonies, repeated references are made to the cleansing (emesis) and purifying properties of these drugs. These observations have lead us to propose the hypothesis that these potions are taken for reasons apart from those that had previously been attributed to them [*i.e.* religious experience, increased sensitivity to the natural world around them, reinforcement of intra-group solidarity, and recreation (Emboden, 1972)]. During the present study we have observed that tropical plants used by South American natives produce an array of isoquinoline and tryptamine-related alkaloids that are not only hallucinogens, but powerful emetics with a wide range of other

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biological activities, in particular antimicrobial and anthelmintic properties (Levin and York, 1977). Since protozoal and helminthic infestations are prevalent throughout the tropics, it is not surprising to find that medicinal plant doctors would select a group of plants that suppress these parasitic organisms.

In this paper, we review the literature and pharmacological data related to the toxicity and chemotherapeutic value of alkaloids to support the hypothesis that psychoactive indole and isoquinoline alkaloids are effective antagonists of the neurotransmitters of the neuromuscular system of helminths, inhibit protozoan parasites and were selected by indigenous plant doctors for their medicinal value.

Evolution of psychoactive drug plants in the tropics

Alkaloids, which number over 5000, have been studied more intensively by pharmacologists than any other plant product because of their great structural diversity and pharmacological activity. The pharmacological and phytochemical literature contains numerous references to the toxicity, neuropharmacological activity, and medicinal value of alkaloids isolated from tropical plants (Farnsworth, 1972; Waller and Nowacki, 1978). The psychoactive alkaloids have also been the subject of many physiological studies, and some of these alkaloids were found to exert a direct neurological effect by antagonizing the effects of important neurotransmitters (Cooper *et al.*, 1978).

LD_{50} data by Levin and York (1977), who compared the effects of different alkaloid skeletal nuclei suggest that those alkaloids containing a structurally rigid nucleus are generally more toxic than those alkaloids with flexible skeletons (for example, strychnine — rigid *vs.* mescaline — flexible). The difference in potency is probably due in part to the reduction of the active conformer by a competitive antagonist at the receptor site (Levin and York, 1977). Some alkaloid skeletal types found to have the lowest LD_{50} values (*e.g.* indole) are also potent hallucinogens (Cooper *et al.*, 1978).

In the study by Levin and York on the ecological significance of alkaloids, a considerable amount of data is presented to show that tropical plants (in particular woody plants) elaborate more toxic alkaloids than their temperate counterparts. The explanation given for that disparity is that tropical plants are exposed to a greater diversity and number of pathogens and herbivores (animals and insects) and therefore those plants containing the most toxic and active alkaloids have been selected for, while others lacking an adequate defense have been eliminated. During the course of evolution, not only was there selection for alkaloids, but there was specific selection for the most toxic skeletal type. Hence, those alkaloids containing an indole, quinoline and isoquinoline nucleus as well as other alkaloid types are widespread in the tropics.

Parasitism in the New World tropics

Parasitic helminth and protozoal infestations are widespread throughout the world, in particular the tropical zones. Mansour (1979), in his review of chemotherapeutic drugs used to fight worms, notes that 650 million people are infested with *Ascaris*, 250 millions with *Filaria* and at least 180 million with *Schistosoma*.

Helminthic infestations (roundworm and flatworm) are generally much higher in the rural areas of the humid tropics. In a series of studies of humid equatorial rural areas of the Americas, the World Health Organization (1978) found that 90 - 98.5% of the populations harbored at least one parasitic species; 66 - 90% had two species or more, and in some areas 60% had three; the only group escaping helminthic infestation were nursing children. The most common organisms were *Trichuris trichiuria*, *Ascaris lumbricoides* and *Necator americanus* (hookworm) (Chandler and Read, 1967). Although helminthic infestations are generally not fatal, they do cause severe anemia, colic and exacerbate malnutrition among people infested by these parasites.

Enteritis and diarrheal diseases generally caused by *Entamoeba histolytica* and some bacteria have been found in studies from 1972 - 1975 to be among the top five causes of death in many countries in tropical America (World Health Organization, 1978). Besides *E. histolytica* other prevalent protozoal pathogens of the gastrointestinal tract are *Chilomastix mesnili*, *Giardia lamblia* and *Trichomonas hominis* (Chandler and Read, 1967).

In lowland tropical areas, such as the Amazon basin, the great majority of the inhabitants suffer from malaria, a parasitic disease of the blood caused by species of the protozoan *Plasmodium*. This protozoan generally kills its hosts and until recently was the leading health problem in the humid tropics (Rollo, 1975). Other protozoal diseases of the blood which are prevalent in the tropics are leishmaniasis, Chagas disease, African trypanosomiases and toxoplasmosis (Chandler and Read, 1967).

Medicinal uses of tropical plants by indigenous peoples

Since synthetic drugs are not readily available to "primitive" cultures of the Amazon, the use of folk remedies for symptoms suggesting parasitic infestations comprise one of the largest shares of the pharmacopeia of the medicinal plant doctors (Morton, 1977). Indigenous people surrounded by an array of different wild plant taxa belonging to different families have selected (by trial and error) those plants which yielded immediate results; *i.e.* they cure illness by expelling parasites. Rubiaceae, which contain isoquinoline alkaloids, are among the most common plant taxa used by tropical natives for emetics.

Cephaelis ipecacuanha, a herb found in the Amazonian forest of Matto Grosso, contains emetine in the roots and is generally taken in powder form or as a syrup. Emetine, which is also an expectorant, is considered to be an

effective remedy against amoebic infections (Gottlieb and Mors, 1978). The genus *Cinchona* (Rubiaceae) elaborates a series of quinoline alkaloids which are effective against *Plasmodium*. These natural drugs were first discovered and incorporated as medicinal potions by plant doctors of the New World tropics and later introduced to the Europeans.

The betel nut (*Areca catechu*, Palmae) from tropical Asia contains arecoline, the alkaloid which is used against tapeworms and roundworms (Morton, 1977). Its juice is also considered to be a mild narcotic and a stimulant (Emboden, 1972).

In surveying the pharmacological and ethnobotanical literature for tropical plants that elaborate anthelminthic alkaloids, it became evident that very little information is available. In contrast, a considerable amount of literature exists on tropical plants that contain psychoactive alkaloids. Schultes and Hofmann (1980) have documented the use of over 30 psychoactive species (in at least ten families) by Amazonian Indians for a variety of reasons. These families include the Rubiaceae, Solanaceae, Malpighiaceae, Acanthaceae, Fabaceae and Apocynaceae. Although very little is known about the medicinal properties of hallucinogenic plants, reports by Schultes and other ethnobotanists who have participated in the drinking of hallucinogenic potions, suggest that besides the expected hallucinatory experience, a plethora of physiological effects accompany the hallucinogenic experience, the most common being vomiting and diarrhea.

On one occasion two of us (E.R. and J.W.) had the opportunity to participate in the drinking of a powerful hallucinogenic drink prepared by Salvador Chindoy, a well-known medicinal plant doctor of the Kamsa Indians of the Upper Putumayo in Colombia. The drink known as *yage* or *ayahuasca* is a dreadful-tasting, reddish-colored decoction prepared from the bark of the vine *Banisteriopsis caapi* (Malpighiaceae). The hallucinogenic potion, which is mixed with an array of "accessory" tropical plants, is imbibed by the plant doctor and then given to the patient in a curative session lasting approximately 8 hours. The yage potion is well-known by Indians from the Upper Orinoco and Rio Negro basins west through the upper Amazon Basin of Colombia, Ecuador, Peru and northern Bolivia (Rivier and Lindgren, 1972; Naranjo, 1979). In talking with Chindoy about the use of yage, he stated that the drink is used to cure an array of physical and mental problems. He further elaborated that the *borrachera* (*i.e.* intoxicating) plant (yage) was taken for the purpose of determining the cause of illness, to help locate lost possessions and to cure patients that are very ill and normally not curable by *nonborracheros* (*i.e.* non-intoxicants). After taking the drink, one might indeed experience an hallucinogenic effect, but the prevalent effects are violent vomiting and diarrhea.

Investigations of other hallucinogenic plants that are prepared as potions or snuffs indicate that common side-effects of psychoactive plants are intoxication, alternation in consciousness, euphoria, nausea, occasional heavy vomiting and frequent diarrhea (Schultes and Hofmann, 1980).

In surveying the chemistry of hallucinogenic plants, it becomes obvious, as previously noted by Schultes (1977), that a large majority of the New World tropical psychoactive plants elaborate alkaloids built on the indole or quinoline skeleton. Quinine and other *Cinchona* alkaloids that have been used for centuries as drugs for suppressing malaria, have various side-effects including blurred vision, disturbed color perception, photophobia and mydriasis (Rollo, 1975).

It is also interesting to note that, by process of trial and error and the possible use of experimental animals (monkeys?), medicinal plant doctors have selected from a plethora of plant species an array of potent drugs with these very unpleasant side-effects for treating ill patients.

Alkaloids and their effects

Besides exhibiting hallucinogenic properties, many alkaloids are powerful antimicrobial agents (Levin and York, 1977). Mitscher *et al.* (1972) determined the antimicrobial activity of 41 alkaloids on the bacteria *Escherichia coli*, *Salmonella gallinarum* and *Klebsiella pneumoniae* and *Candida albicans* (yeast). The alkaloid types found to be most effective against microorganisms were the indole and bensoisoquinoline alkaloids.

Traditional and modern chemotherapy of helminthic infestations include a variety of synthetic and natural drugs. A majority of those drugs are alkaloids which not only destroy the parasitic worms but also play a role in expelling the worms. For example, pyrazine, a synthetic alkaloid, causes paralysis of *Ascaris* by inhibiting synaptic transmissions by hyperpolarization of membranes (Mansour, 1979). Arecoline, as noted before, causes paralysis of muscle movements in *Cestodes*. Besides their neuromuscular effects on the parasites, many anthelmintics exert numerous side-effects on the patient's central nervous system. Phenothriazine, a compound obtained by fusing phenylamine with sulfur, is a widely used and very active anthelmintic, but it is not recommended for humans because of the violent hallucinatory effects observed at the effective dosages (Castillo, 1969). Bephenium, a quaternary ammonium compound, is effective against nematodes which inhabit the intestine, but it may cause nausea, vomiting, and abdominal pain (Castillo, 1969). The natural drugs emetine and quinine also exhibit bad side-effects, such as hallucinations and nausea, if given in excessive dosages (Rollo, 1975).

The above-mentioned anthelmintics effect parasitic worms in numerous ways. They either kill, dislodge or paralyze helminths by interfering with important biochemical and physiological processes. The helminth neuromuscular system, as noted by Mansour (1979), utilizes the neurotransmitters acetylcholine and serotonin. Serotonin receptors present in several species of flatworms are important in the regulation of motility and carbohydrate metabolism and in activating adenylate cyclase. Serotonin is present in rather

large quantities in the human intestine, and flatworms regulate their metabolism by host hormones; schistosomes have been reported to have an uptake mechanism for serotonin (Mansour, 1979). In a highly coevolved relationship this is certainly understandable, since an existing parasite would have integrated its metabolism with that of its host.

Mansour (1979) has established that a powerful antagonist of serotonin in the parasite metabolism is the hallucinogen *d*-LSD. On worms, LSD antagonizes the stimulant action of serotonin and depresses the activity of adenylate cyclase. Exactly how *d*-LSD antagonizes serotonin is unknown, but one could suggest that it might compete with serotonin receptor sites present on the membranes of worms.

Although little comparative data are available on the effects of naturally occurring psychoactive drugs on parasitic worms, it seems plausible to suggest that many alkaloids having an indole and isoquinoline nucleus (and are hallucinogenic) may indeed exhibit potent anthelmintic properties. It also seems probable that indigenous people of the New World tropics have noticed a correlation between psychotropic effects of these alkaloids and the alleviation of symptoms caused by parasitic worms and protozoans and thus used the former as a dosage indicator.

In order to test our hypothesis concerning protozoal parasites one of us has developed an *in vitro* chemical screening test to determine the effects of various alkaloids against *Trypanosoma cruzi* (Chagas disease) epimastigote forms (Cavin, in preparation). Those alkaloids with marked effects (over 70% inhibition after 96 hours) included harmine, quinine hydrochloride, vinblastine sulfate, emetine dihydrochloride and atropine. Arecoline and berberine, which are employed as anthelmintics, showed 40% inhibition after 96 hours.

Concluding remarks

In this brief review, we have examined the etiology of hallucinogenic plant use from a medicinal perspective. We conclude, from our personal observations and from ethnobotanical and pharmacological data, that Amazonian plant doctors could have selected potent psychoactive drug plants in part to control parasitic outbreaks. These potions, a complex mixture of organic chemicals, contain antiparasitic alkaloids with an indole or isoquinoline nucleus. We propose that these alkaloid mixtures were initially discovered and developed by indigenous people for treatment of a variety of parasitic diseases and incorporated into religious ceremonies using psychoactivity as an effective dose marker. Although the discussion has been limited to the New World tropics, it is possible that similar compounds are also used in the Old World as anthemintics or that a different group of chemicals and plants have been developed as a source of anthelmintics.

It is clear from this preliminary investigation that further studies are needed to establish the etiology of tropical psychoactive plants as anthelmintics and antiparasitic agents. Multidisciplinary studies will undoubtedly provide new and natural sources of anthelmintic drugs.

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