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Lausanne, April 14, 1980

To: Dr. Plutarco Naranjo
Sociedad Latinoamericana de Farmacología
Casilla 2339
Quito
Ecuador

Dear ~~Colleague~~, Plutarco

I should very much appreciate your reviewing the enclosed

manuscript by E. Rodriguez et al.

entitled: The Role of Amazonian Psychoactive Drug-Plants in the Chemotherapy of Parasitic worms

I am enclosing for your convenience a referee's check list. This list suggests some criteria for evaluation of the paper and is for the editor's use. Please write your detailed comments on a separate sheet of paper that does not reveal your identity or affiliation.

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With many thanks for your assistance,

Best Regards.

Laurent

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The role of Amazonian psychoactive drug-plants in the chemotherapy of parasitic worm.

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INTRODUCTION

Over the last half century investigations by ethnobotanists have shown that the use of psychoactive drug-plants by indigenous peoples of tropical American 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 drug-plants are taken for reasons apart from those that had previously been attributed to them (e.g. religious experience, increased sensitivity to the natural world around them, reinforcement of intra-group solidarity, and recreation). In our study we have found that drug-plants used by South American natives produce an array of isoquinoline and tryptamine alkaloids that are not only hallucinogens, but powerful emetics with a wide range of biological activities, in particular antimicrobial and anthelmintic properties (Waller and Nowacki 1978). Since protozoal and helmintic infestations are very prevalent throughout the tropics, it is not surprising to find that medicinal plant doctors would select a group of drug-plants that suppress these parasitic organisms.

In this paper we present recent ecological 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 neuromuscular system of parasites and were probably selected by indigenous plant doctors because of 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 tropical alkaloids (Waller and Nowacki, 1978; Farnsworth, 1972). The psychoactive alkaloids have also been the subject of many physiological studies, and some alkaloids were found to directly exert a neurological effect by antagonizing the effects of important neurotransmitters (Figure 1).

Comparative LD_{50} data for different alkaloid skeletal nuclei suggest that those alkaloids containing a structurally rigid nucleus are generally more toxic than those alkaloids with flexible skeletons (e.g. strychnine vs. mescaline). The differences in potency is due in part to the reduction of the active conformer at the receptor site (Levin and York, 1977). Interesting enough, some alkaloid skeletal types found to have the highest LD_{50} values (e.g. indole) are also powerful hallucinogens.

In a study by Levin and York (1977) on the ecological significance of alkaloids, the two investigators present a considerable amount of data 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 (hallucinogenic?) skeletal type. Hence, those alkaloids containing an indole, quinoline and isoquinoline nucleus are widespread in the tropics, but other alkaloid types are also present. Indigenous people surrounded by an array of different wild plant taxa belonging to different families have selected those plants which yielded

immediate results - i.e. they cured illness by expelling parasites. A large portion of those plants also contain neuron atagonists that induce hallucinations.

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 excellent review of chemotherapeutic drugs used to combat worms, notes that 650 million people are infested with Ascaris, 250 million 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 equitorial rural areas of Indonesia, 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, it is interesting to note that the only group escaping helmintic infestation were nursing children. The most common organisms were Trichuris trichiuric, Ascaris lumbricoides and Necator americana (hookworm) (Chandler and Read, 1967). Although helmintic infestations are generally not fatal but they do cause severe anemia, colic and exacerbate malnutrition among people infested by these parasites.

Enteritis and diarrheal diseases generally caused by Entameba histolytica have been found in recent studies (from 1972-1975) to be among the top 5 causes of death in many countries in tropical America (Who, 1978). Besides A. histolytica other prevalent protozoal pathogens of the gastro-intestinal 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 host and at one time was recognized as the leading health problem in the humid tropics (Rollo, 1975). Other protozoal diseases of the blood which are great importance 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 "primitive" folk remedies for parasitic infestations are legion and comprise one of the largest shares of the pharmacopia of the medicinal plant doctors (Lewis and Alvin-Lewis, 1977). Plant taxa of the Rubiaceae which contain isoquinoline alkaloids are among the most common plants used by tropical natives for emetics. Cepahaelis ipecacuanha, an herb found in the Amazonian forest of Matto Grosso, contains the amebicide emetine which is present in the roots and is generally taken in powder form or as a syrup (Figure 2). Emetine is an expectorant and is considered to be an effective remedy against amebic infections (Gottlieb and Moss, 1979). The genus Cinchona (Rubiaceae) elaborates a series of quinoline alkaloids which are effective against Plasmodium, the malarial parasite. These natural alkaloids were first discovered and prepared into medicinal potions by plant doctors of the New World tropics and later introduced to the Europeans.

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

In researching the pharmacological and ethnobotanical literature for tropical plants that elaborate anthelmintic alkaloids, it becomes evident that very little information is available. On the other hand, a considerable amount of literature is available on tropical plants that contain pyschoactive alkaloids that cause alterations in consciousness. Schultes (1977) in his monumental research on Amazonian plants that contain psychoactive alkaloids, has documented the use of over 30 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. In one occassion we (ER and JW) had the opportunity to participate in the drinking of a powerful hallucinogenic potion prepared by Salvador Chindoy, a well-known medicinal plant doctor of the Kamsa Indians of the Upper Putumayo in Colombia. The drink known as yagé or ayahuasca is a dreadful reddish-colored drink prepared from the bark of the vine Banisteriopsis caapi (Malpighiaceae). The drug-plant potion, which is mixed with an array of "accessory" tropical plants (many of which are unknown), is taken by the plant doctor and then given to the patient in a curative session lasting 8 hours. The medicinal yage potion is well-known throughout the Amazon, with indians extending from the Upper Orinoco and Rio Negro west through the upper Amazon Basin of Colombia, Ecuador, Peru and south to northern Bolivia using the drink for religious, ritual and medicinal purposes (M. Mathias, personal communication). In talking with Chindoy about the use of yagé, he noted that the drink is

used to cure an array of physical and mental problems. He further elaborated that the "borrachera" plant (yagé) 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". After taking the drink, one might experience a hallucinogenic effect, but the prevalent effects are violent vomiting and diarrhea. There is no question in my mind, that if yagé is prepared incorrectly, it can be a deadly neurotoxin!

Investigations of other hallucingoenic plants that are prepared as potions or snuffs indicate that common side effects of psychoactive drug-plants are intoxication, alteration in consciousness, euphoria, nausea, occassional heavy vomiting and frequent diarrhea.

Besides exhibiting mind-expanding properties, many alkaloids are powerful antimicrobial agents (Levin and York, 1977). Mitscher and associates (1972), determined the antimicrobial activity of 41 alkaloids on the bacteria Escherichia coli, Salmonella gallinarum, Klebsiella pneumoniae and Candida albicans (yeast). Alkaloid types found to be most effective against microbes were the indole and bensoisoquinoline alkaloids. Quinine and other Cichona alkaloids have been used for centuries as drugs for suppressing malaria. Common side effects of quinine are blurred vision, disturbed color perception, photophobia and mydriasis (Rollo, 1975).

In surveying the natural products chemistry of psychoactive drug-plants, it becomes obvious (as previously noted by Schultes, 1977), that a large majority of the New World tropical psychoactive drug-plants elaborate alkaloids built on the indole or quinoline skeleton. 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 neurotoxins for treating ill patients.

Amazonian psychoactive alkaloids and their possible effects on parasitic worms

Traditional and modern chemotherapy of helmintic 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, a natural alkaloid from the betel nut causes paralysis of muscle movements in Cestodes. Besides their neuromuscular effects, many synthetic and natural 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 anthelmintic because of its high activity, but is not recommended for humans because of violent hallucinatory effects observed at the effective dosages (Castillo, 1969). Bephenium, a quaternary ammonium compound, is effective against nematodes which inhabit the intestine, but may cause nausea, vomiting, and abdominal pain (Castillo, 1969). The natural drugs emetine and quinine also exhibit bad side-effects (primarily on the CNS) 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, carbohydrate metabolism and activating adenylate cyclase. Serotonin is present in rather large quantities in the human intestine, and flatworms regulate their metabolism by host hormones; schistosomes having been reported to have an uptake mechanism

for serotonin (Mansour, 1979). This is certainly understandable, since a parasite existing in a highly coevolved relationship would have integrated its metabolism with that of its host.

Comparative studies by Mansour (1979) with an array of chemotherapeutic agents have established that a powerful antagonist of serotonin is the natural hallucinogen, d-LSD. 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 is 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 tropic have noticed a correlation between psychotropic effects of these alkaloids and the alleviation of symptoms caused by parasitic worms and protozoans.

Concluding Remarks

In this brief review, we have closely examined the etiology of psychoactive drug-plant use from a medicinal perspective. We conclude, from our personal observations, ethnobotanical, ecological and pharmacological data; that Amazonian plant doctors have also selected potent psychoactive drug-plants to control parasitic outbreaks. These drug-plants potions, consisting of a complex mixture of organic chemicals, contain as the major anthelmintics alkaloids containing 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 diseases and later incorporated into religious ceremonies. 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 anthelmintics or a different group of chemicals and plants have been developed as a source of anthelmintics.

It is clear from our preliminary investigation that further ethnopharmacological studies are needed by temperate scientists to establish the etiology of tropical psychoactive drug-plants as anthelmintics and anti-protozoal agents. Multidisciplinary studies will undoubtedly provide new and natural sources of anthelmintic drugs.

Acknowledgements

We sincerely express our gracias to Salvador Chindoy, a Kamsa Indian and Doctor of Medicinal Plants of the Upper Putomayo (Amazon Valley of Sibundoy), who provided the initial impetus and natural insights for this study. It is hoped that in future studies by ethnopharmacologists, credit will be given to those marvelous Plant Doctors of the Amazon who through a scientific method unknown to western man, have made numerous discoveries of drug-plants and shared them with westerners. E.R. also thanks Dr. Bernardo Ortiz de Montellano (Wayne State University) and Dr. G.H.N. Towers and Dennis McKenna (Univ. of British Columbia, Vancouver Canada) for their stimulating ideas and constructive criticism of this manuscript. We also thank Elizabeth Baez (UCI) for her assistance in preparing the manuscript and UCI Faculty Research Grant and the Undergraduate School for financial support.

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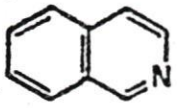
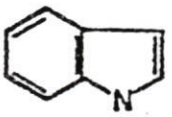
FIGURE 2

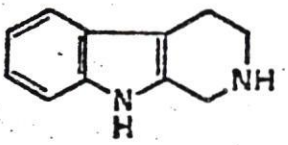
POTENT EMETICS AND HALLUCINOGENS OF THE TROPICS



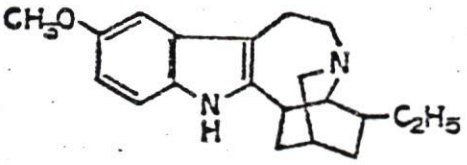
Isoquinoline



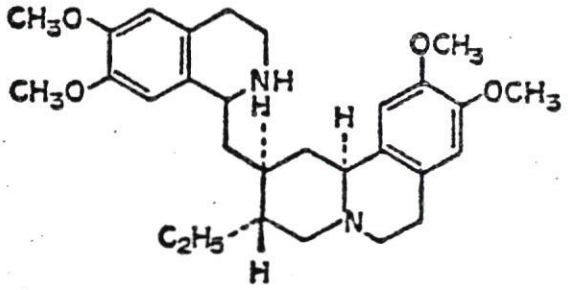
Indole



B-carbolines
(Banisteriopsis)



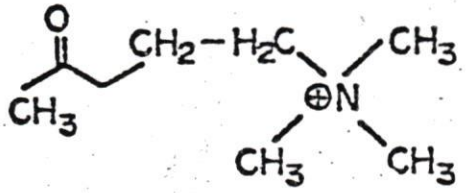
Ibogaine
(Tabernanthe)



Emetine

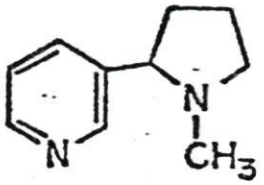
FIGURE 1

STRUCTURAL RELATIONSHIP OF ALKALOIDS TO NEUROTRANSMITTERS



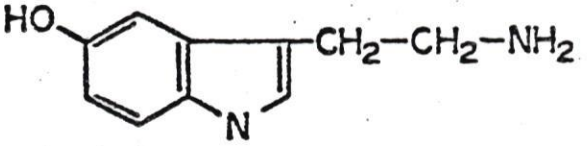
Acetylcholine

≡



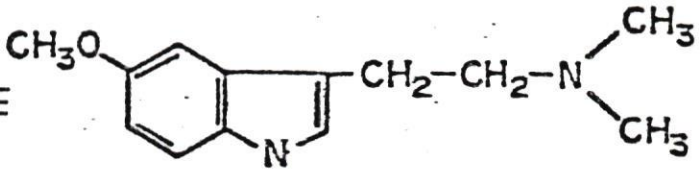
Nicotine

∴ Depolarizing action



Serotonin

≡



5-Methoxydimethyltryptamine

∴ Prolongs serotonin level in brain by blocking monoamine oxidase