On the Comparative
Ethnopharmacology of
Malpighiaceous and
Myristicaceous Hallucinogens

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This article discusses comparative ethnographic, ethnomedical, phytochemical and pharmacological aspects of two Amazonian hallucinogens. The hallucinogenic drink ayahuasca is prepared from the liana Banisteriopsis caapi (Malpighiaceae) and sundry admixture plants, notably Diplopterys cabrerana and various Psychotria spp. (Schultes 1957). The cambial resin of certain members of the genus Virola (Myristicaceae) is the source of hallucinogenic snuffs and orally ingested hallucinogenic pastes used by some tribes (Schultes 1979).

Although derived from entirely different botanical sources, similar alkaloids — tryptamines and β-carbolines — are the active constituents of both preparations. In the case of ayahuasca and the orally ingested Virola pastes, it has been suggested that monoamine oxidase (MAO) inhibition — due to the β-carbolines — protects the hallucinogenic tryptamines from oxidative deamination by peripheral MAO and thus permits their oral activity (Schultes 1972, 1969; Der Marderosian, Pinkley & Dobbins 1968). Experimental investigations of this postulated mechanism of oral activity — involving in vitro evaluations of the drugs and their constituents as MAO inhibitors (MAOi) — have been reported in other articles (McKenna, Towers & Abbott 1984a, 1984b). The present article summarizes the results of these comparative studies of ayahuasca and the Myristicaceous hallucinogens. Complete details of these phytochemical and pharmacological investigations may be found in McKenna, Towers & Abbott (1984a, 1984b).

AYAHUASCA

The contemporary use of ayahuasca in South America occurs primarily within the context of mestizo folk medicine, which is comprised of amalgams of many tribal traditions. Although most of these tribes have long since fragmented or disappeared, much of their ethnobotanical lore has survived and been adopted by the mestizos. Ayahuasca is part of this lore and it occupies a central and important position in mestizo folk medicine. Not only is it employed as a general cure-all for the treatment of many disorders ranging from mental illness to parasites, it is also the ayahuasca-qeuro’s or healer’s passport to supernatural dimensions where the skills intrinsic to the healer’s profession can be acquired. It enables the healer to learn the medicinal uses of plants — as well as the songs and chants used in the healing ceremonies — with which the healer is able to diagnose diseases, divine the supernatural causes of illness, predict the future, and see and communicate across distances. Whether or not there is a rational basis for any of these practices, an impressive pharmacopoeia of plants — many of which do contain highly biodynamic constituents — is (or can be) used in conjunction with ayahuasca (McKenna, Luna & Towers 1984).

Phytochemical investigations (McKenna, Towers & Abbott 1984a) have found that most mestizo ayahuasca brews contain substantial amounts of β-carbolines and

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N,N-dimethyltryptamine (DMT). The major β-carboline is harmine and tetrahydroharmine, with lesser amounts of harmaline. Only traces of other β-carbolines were detected. The amounts of β-carbolines in these samples were several orders of magnitude greater than those reported in an earlier study of ayahuasca prepared by tribes inhabiting the upper Rio Purús in southwestern Peru (Rivier & Lindgren 1972). A typical 100 ml dose of mestizo ayahuasca contains between 500 and 800 mg β-carbolines and 40-80 mg DMT. This is well above the hallucinogenic threshold dose for DMT and within the range at which the β-carbolines are effective MAOIs. However, it is still well below the threshold level for hallucinogenic activity of the β-carbolines. Therefore these data indicate that the hallucinogenic activity of ayahuasca is probably due to DMT, which is orally activated by some mechanism, presumably the MAO inhibition induced by the high concentration of β-carbolines. This hypothesis is supported by the finding that ayahuasca is a very effective inhibitor of MAO in vitro even when diluted by many orders of magnitude (McKenna, Towers & Abbott 1984a).

A number of ayahuasca samples, brewed by different practitioners in different parts of Peru, were analyzed. Although the same alkaloids were consistently found, the samples differed mainly in the concentration and proportions of various components. Concentration differences are expected as this is dependent on the amount of plant material extracted and other variables in the preparation procedure. Proportional differences may be attributable to the use of different B. caapi cultivars. It is remarkable that, faced with so many variables, ayahuascaqueños all across Peru manage to manufacture a drug having a high degree of pharmacological consistency from batch to batch. Except for concentration and proportional differences, all of the ayahuasca samples analyzed could have been taken from the same pot. All of the DMT-containing admixture plants that were analyzed were similar and DMT was the single major base in all of them, while only traces of other alkaloids were detected. The concentration of DMT was between 1.0-2.0 mg/g dry weight in all samples. Similar consistency was not found in the several B. caapi cultivars that were analyzed. More or less the same constituents were present, but concentrations ranged from 1.7 mg/g dry weight (total alkaloids) to 13.6 mg/g dry weight. These differences probably are due to environmental factors rather than to genetically based biochemical differences between cultivars.

**MYRISTICACEOUS HALLUCINOGENS**

Unlike ayahuasca, the use of hallucinogenic prepara-

**HALLUCINOGENS**

...tions derived from Virola spp. or other Myristicaceous genera is a practice confined to a few indigenous Amazonian tribes and has never become integrated into mestizo folk medicine (Schulz 1979). As a result, the use of these Myristicaceous drugs has diminished or in some cases disappeared as the tribal societies have fragmented due to outside influences. This is particularly true of the orally ingested Myristicaceous pastes. Use of Virola spp. as an oral hallucinogen is more ethnologically restricted than its use as a snuff. It has been reported among the Bora, Witoto, Muinane and possibly the Maku, but apparently does not occur outside these groups. Even within these tribes, the source plants, methods of preparation and modes of usage of the oral Virola drug are the specialized knowledge of the healers and are not known to most members of the tribe. Another complicating factor is that the Bora and Witoto populations inhabiting the Rio Ampiyacu region, where the fieldwork for this study was carried out, are not indigenous to that area but migrated there from north of the Rio Putumayo in the early decades of this century, as a result of the dislocations produced by the rubber industry. This has not contributed to the preservation of their ethnomedical traditions nor any other tribal institutions. The result is that local knowledge of the oral Myristicaceous drugs has become, in some cases, rather inexact.

Work reported elsewhere (McKenna, Towers & Abbott 1984b) has shown that there is a high degree of variability in the type and amount of alkaloid constituents, not only among different Virola spp., but even among different collections of the same species. The composition of the orally ingested paste samples that were analyzed was similarly variable, both qualitatively and quantitatively. Presumably this is a reflection of the chemical variability of the source plants. Thus, while all of the ayahuasca samples had essentially the same constituents (with DMT being present or absent, depending on which Psychotria sp. was used as admixture), not one of the oral Virola pastes had the same base composition as any other one. Large differences in the concentration of alkaloids in various samples were also found. Either this high degree of chemical variability has always been a feature of these orally ingested pastes or the criteria that were formerly used to select the strongest Virola species to prepare the paste (e.g., taste, smell and/or visual appearance of the resin) have been largely forgotten and the selection now has become a fairly haphazard process. If the former possibility is true, this may explain why the paste was restricted to the healers and why they usually consumed it alone. If only one out of every three or four samples actually is orally...
active, this information was probably kept from the people at large, in order to preserve their faith in the efficacy of the healer and the medicines.

Another objective of these investigations was to examine the mechanism for the (presumed) oral activity of these Myristicaceous pastes: is it due, like ayahuasca, to the oral activation of the tryptamine constituents through the inhibition of visceral MAO by β-carbolines? In the process of answering some of these questions, these investigations have created new and even more puzzling ones. In the first instance, β-carbolines were not consistently found as constituents of all of the paste samples. Even in the two samples containing β-carbolines, only traces were detected. Those β-carbolines that were found belong to the tetrahydro-β-carboline type, which are poor MAOIs compared to the dihydro- and fully aromatic β-carbolines. A further point is that the presence or absence of β-carbolines in the past samples apparently had little or nothing to do with their oral activity or inactivity as determined by self-experiments (McKenna, Towers & Abbott 1984b). The paste sample that contained the highest levels of β-carbolines was completely inactive in repeated self-experiments. Another sample that contained only high concentrations of 5-methoxy-N,N-dimethyltryptamine (5-MeO-DMT) in the base fraction was highly orally active, although the activity was not typical of hallucinogens. Although the Myristicaceous paste samples did exhibit some degree of MAO inhibition, this was shown to be primarily, if not entirely, due to the tryptamine constituents, while nonalkaloidal constituents from the samples showed only a slight degree of nonspecific inhibition (McKenna, Towers & Abbott 1984b). Most of the synthetic tryptamine derivatives that were assayed as MAOIs did exhibit some activity, but the IC₅₀ values were usually several orders of magnitude lower than those for the β-carboline derivatives. Interestingly, DMT showed the most MAO activity of all the tryptamine derivatives tested: Its IC₅₀ was comparable to tetrahydroharmine (THH), one of the least active of the β-carbolines. All of this evidence considered together suggests that the Myristicaceous pastes, when they are orally active, must owe their activity to some mechanism other than MAO inhibition, whether due to β-carbolines or other constituents.

What alternative mechanism might account for oral activity of some samples? There are basically two possibilities worth consideration and both would require further experimental investigations to confirm them. The first is that the oral activity of the Myristicaceous pastes is not due to the tryptamines at all, but rather to some other biologically active constituents, such as lignans (phenylpropanoid dimers). Certainly this would help to explain why the oral activity observed in self-experiments was atypical for hallucinogens. It is equally possible, however, that tryptamines taken orally differ significantly in their effects from tryptamines administered parenterally. That Virola resin (including the sample assayed) does contain biologically active lignans has been established (MacRae & Towers 1984a), but whether or not these lignans are capable of eliciting the spectrum of biological responses observed in the bioassay is not known. The second possibility, which also calls for much further experimental investigation, is that the oral inactivation of DMT, 5-MeO-DMT and related derivatives is not due to oxidative deamination by peripheral MAO. Alternative metabolic pathways may be relatively more significant in the degradation of these compounds in peripheral tissues.

Both in vitro and in vivo studies of DMT metabolism (Barker, Monti & Christian 1980; Szara & Axelrod 1959) suggest that 6-hydroxylation and/or N-oxidation of DMT occurs more readily in peripheral tissues than deamination by MAO. 6-Hydroxylation has been shown to occur in peripheral tissues, but apparently not in the brain (Barker, Monti & Christian 1980; Szara & Axelrod 1959). Significantly, 6-hydroxy derivatives of DMT and related compounds are inactive as hallucinogens (Shulgin 1976). Little is known of the hallucinogenic action of N,N-dimethyltryptamine-N-oxide (DMT-NO), but if it follows the general pattern for tertiary amine N-oxides (Bickel 1969), it would either be completely inactive or 10 to 100 times less active than DMT. Other studies of in vivo DMT metabolism in the presence of MAOIs and microsomal mixed function oxidase (MFO) inhibitors (Shah & Hedden 1977) have found that while the MFO inhibitor SKF-525A does not. The authors interpret these results as support for the hypothesis that DMT is metabolized mainly by MAO in vivo.

A problem with most in vivo studies of the type reported by Shah and Hedden is that the DMT is administered to the animal intraperitoneally rather than orally, thus the compound reaches the circulation directly and avoids intestinal/hepatic-portal shunt metabolism. It is possible that the metabolism of DMT via the intestinal/hepatic-portal shunt may differ in important respects from its metabolism when introduced directly into the bloodstream or body cavity. In the hepatic shunt, 6-hydroxylation and/or N-oxidation may be more important than MAO as a catabolic route for the compound. In any event, in vivo metabolic studies involving intraperitoneal or other parenteral routes of administration actually shed little light on DMT metabo-
The fact is that current understanding of the peripheral metabolism of DMT and related compounds is far from complete. All that is known for certain is that more than one type of oxidative reaction is involved. MAO may be partially responsible for the degradation of tryptamines in the periphery, but microsomal MFOs, which are involved in both the 6-hydroxylation and N-oxide pathways, are possibly even more important. Interestingly, if orally administered DMT is a substrate for microsomal oxidases, then a mechanism can be proposed to explain the oral activity of some Virola pastes, even though they lack β-carbolines and are not significantly effective as MAOIs. This alternative mechanism postulates that some of the nonalkaloidal constituents in the pastes may possess antioxidant activity and/or exhibit activity as specific inhibitors of microsomal MFOs. In the former case, presence of high concentrations of nonspecific antioxidants could scavenge a high proportion of the molecular oxygen in the vicinity, thus making less of it available as cosubstrate for the microsomal enzymes catalyzing DMT N-oxidation and 6-hydroxylation. In the latter case, constituents in the Virola resin may specifically inhibit hepatic microsomal MFOs and thus block the oxidation(s) of DMT caused by these enzymes. In either case, the compound could be protected from oxidative transformation in the intestinal/hepatic shunt and thus be taken up into the central nervous system (CNS) in the form of the unchanged tertiary amine.

A number of lignans have been characterized that exhibit protective activity against hepatotoxins (MacRae & Towers 1984b); inhibition of hepatic MFO has been proposed as the probable mechanism. All of the active compounds possessed a methylenedioxyphenyl moiety, but analogues lacking this configuration did not have hepatoprotective properties. The methylenedioxyphenyl group has been implicated in other studies as the main pharmacophore responsible for MFO inhibition (Bratsten 1977). The Myristicaceae genera Virola and Iryanthera are both rich in constituents incorporating the methylenedioxyphenyl group, including fatty acid derivatives, neolignans, flavones and diarylpropanoids (Gottlieb 1979).

Several novel lignans having this substitution were characterized in the bark of DMK-59 (V. elongata), which was the source plant for the paste sample that showed the greatest degree of oral activity in self-experiments (MacRae & Towers 1984a; McKenna, Towers & Abbott 1984b). A number of other phenolic compounds, including flavones, flavonoids, isoflavonoids, diarylpropanoids and neolignans, have been isolated from a number of Virola and Iryanthera spp. Some of these compounds could act as antioxidants and could contribute to the inactivation of MFOs via this nonspecific mechanism. In any case, the peripheral metabolism of DMT and related compounds, following oral administration, may be significantly altered in the presence of antioxidants and/or specific MFO inhibitors. Under these conditions, the compound might well reach the CNS in the form of the unchanged tertiary amine. Further in vivo and in vitro experiments would be required to confirm or disprove this alternative mechanism of oral activity. In view of the phytochemical and pharmacological data accumulated in the present study, it appears that this alternative hypothesis is at least as probable—if not more probable than MAO inhibition—as the mechanism responsible for the oral activity of the Myristicaceae pastes.

CONCLUSION

Phytochemical and pharmacological information collected in the course of these authors' studies has been insufficient to definitely establish the mechanism of oral activity in two Amazonian hallucinogens. However, it has provided phytochemical data and in vitro pharmacological evidence that indicates, in the case of ayahuasca, that the original hypothesis proposed to explain the oral activity has not been disproved. Certainly ayahuasca contains high enough concentrations of β-carbolines to effectively inhibit MAO and by this mechanism the active hallucinogenic constituent DMT may be protected from peripheral degradative metabolism. The alternative mechanism proposed in the above discussion may also be implicated in the pharmacology of ayahuasca, but at least it is not necessary to invoke this mechanism for ayahuasca. In the case of the orally ingested Myristicaceae preparations, however, these investigations indicate that MAO inhibition—whether due to β-carbolines or some other constituents—is almost certainly not the mechanism responsible for their oral activity. The pastes do not contain more than traces of β-carbolines, they show poor activity as MAOIs and their oral activity, when present, is not correlated with the presence of β-carbolines. Some alternative mechanism must therefore be invoked to explain the oral activity of these Myristicaceae pastes. Two such alternatives have been discussed above. One is that the oral activity is due to biologically active constituents other than tryptamines. The other possibility is that the active tryptamines are protected from peripheral degradation by constituents that inhibit hepatic MFOs, the enzymes responsible for 6-hydroxylation and N-oxidation of tryptamine derivatives. MFO inhibitors require the presence of a methyl-
enedioxyphenyl configuration as the active pharmacophore, and *Virola* spp. are excellent sources of compounds possessing this moiety. Unfortunately, neither alternative mechanism can be proven or disproven until more has been learned about the in vivo metabolism of DMT and related compounds. An obvious place to start would be to study the metabolism of orally administered DMT in the presence of known MFO inhibitors.

**REFERENCES**


