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Editorial

Understanding the chemical language of the natural pharmacopeia: Whose hallucinogen is it anyway?

Humans communicate aggression through words, gestures, guns, bombs, and missiles. Guns, bombs, and missiles are left out of expressions of affection, unless they are meant to impress a loved one or affirm a beloved ideology. Many organisms other than humans use gestures although they may not have words, and the vast majority of organisms also use the language of chemistry in offence and defence.

Secondary metabolites make up most of the lexicon of this language. They are termed secondary to be differentiated from primary chemicals that govern basic metabolic functions. The lower the trophic level, the greater the diversity of secondary metabolites. There are, therefore, few toxic birds and venomous mammals. However, sessile organisms such as plants, corals, sponges, and fungi have impressive arrays of secondary metabolites to counter hostile biotic and abiotic conditions that they encounter while being rooted to the ground or cemented on to a reef and unable to move to resist attacks or to find greener pastures.

This vast natural pharmacopeia has traditionally been viewed from the lens of natural products chemistry. The questions that have been asked of these molecules have revolved around their usefulness for humans. Their natural roles (e.g., Pawlik *et al*. 2007) have been largely ignored, although there are now calls for a chemical ecology perspective on this whole arsenal of potential drugs (Petersen *et al*. 2020; Galitz *et al*. 2021).

A few examples should illustrate this point more forcefully. Australia has recently sanctioned the use of psilocybin in human therapeutics for depression and other neuro-psychiatric disorders, and it is the first country to do so, despite misgivings about its real benefits. Psilocybin is a molecule that has hallucinogenic effects in humans. Psilocybin is produced by basidiomycete mushroom fungi. It is a non-selective agonist of many serotonin receptors. While studies of the human use of psilocybin are in the thousands, those on their chemical ecology, especially in the *Psilocybe* genus of mushrooms are sparse and still speculative (Meyer and Slot 2023). Which organisms are meant to be targeted by psilocybin and by psilocin, another common metabolite in these mushrooms? The first record of learned aversion to the muscimol hallucinogen in *Amanita muscaria* mushrooms came from the nocturnal opposum *Didelphis virginiana* (Camazine 1983). Muscimol is a gamma-aminobutryic (GABA) agonist in vertebrates. Besides hallucinogens in mushrooms, there are the many cases of *Amanita* mushrooms, e.g. *A. phalloides*, being used in famous murders such as the one committed by Agrippina who poisoned her husband the Roman emperor Claudius with an extract of the death cap mushroom that was apparently added to the emperor's favourite dish of *boleti* (what the Romans called the non-poisonous *Amanita caesarea*) either by the emperor's food taster or by the empress herself. *Amanita phalloides* contains α-amanitin, a tasteless but toxic peptide that takes effect after several hours. The beloved writer of murder mysteries Dorothy Sayers apparently got it wrong in *The Documents in the Case* when the murderer used synthetic muscarine, derived from *Amanita muscaria*, in the stock used to prepare a stew. Muscarine is destroyed by cooking and Sayers and co-author Robert Eustace clearly needed to know their chemistry (Wasson 1972); the victim would have lived to tell the tale.

It is puzzling that toxic and edible mushrooms often cannot be told apart, leading to many accidental poisonings. Aposematism, or warning colouration, is believed to have evolved in toxic organisms such as frogs and insects to warn potential predators, and provides honest signals of unpalatability (Caro and Ruxton 2019). Is olfactory aposematism (Eisner and Grant 1981), leading to deterrence and repellence, possible in mushrooms?

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And is it just that humans are unable to sense these warning molecules while the organisms for whom the signals are intended comprehend this chemical language and stay clear? We have obviously much to learn about these compounds in their natural contexts. Budding Feludas must beware.

The sesquiterpene lactone artemisinin is another mystery. The Nobel Prize in Physiology or Medicine was awarded to Youyou Tu in 2015 for her discovery of artemisinin's efficacy in the treatment of malaria. Artemisinin was isolated from *Artemisia annua*, native to China. The genus *Artemisia* in the family Asteraceae has close to 500 species, some of which are used as herbs in European cuisine, e.g., tarragon, *Artemisia dracunculus*. Yet, the chemical ecology of *Artemisia* is largely unknown, and certainly the raison d'être for artemisinin, a sesquiterpene lactone, in *A. annua* is yet to be discovered while *Plasmodium* is already resistant to artemisinin in many parts of Asia. Several species of *Artemisia* occur in India and while work on the chemical ecology of these species has begun, the results are awaited. Even in its native range, populations of *A. annua* vary in their content of artemisinin; consequently, the WHO has issued a directive that consumption of leaves of *A. annua* are an inadequate treatment for malaria, since the provenance of the plant population matters for artemisinin. Why this should be so is as yet unknown. Sesquiterpene lactones are characteristic of the Asteraceae and have been characterised to have anti-helminthic and anti-parasitic activity (Picman 1986). These lactones can also occur together with other potent anti-helminths such as steroid glucosides; wild chimpanzees are reported to self-medicate on the pith of stems of *Vernonia amygdalina*, another herb in the Asteraceae, that contains high concentrations of these glucosides (Ohigashi *et al*. 1994).

Another fascinating compound in the human arsenal against debilitating conditions such as Parkinson's disease is dopamine or its precursor L-DOPA. Humans and many animals make L-DOPA from the amino acid tyrosine and it is vital for nervous system functioning. However, many plants make L-DOPA in large quantities, and here too, its natural functions remain to be discovered. A valuable natural source of L-DOPA is *Mucuna pruriens*, also called the velvet bean, native to Africa and Asia. Preliminary work seems to indicate that several insects appear to be able to tolerate high doses of L-DOPA and are able to successfully consume the seeds and leaves. Is L-DOPA the target molecule for the insects or for mammals that may consume the seeds? Many varieties of *M. pruriens* also have pods that are covered with urticating hairs called trichomes. Is there a relationship between L-DOPA and trichomes? Does one defence preclude the other? These and many other questions remain unanswered.

Natural products chemistry coupled with chemical ecology will help targeted investigations and fewer fishing expeditions. Secondary metabolites are the result of trillions of chemical experiments in the evolution of life. The parsing of verbs, and the identification of nouns, and the syntax of sentences in the chemical language of the natural world must go forward in tandem.

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Renee M. Borges,
Editor-in-Chief, Journal of Biosciences,
Centre for Ecological Sciences,
Indian Institute of Science,
Bengaluru 560012, India
(Email, renee@iisc.ac.in)