# Short Communication

## PSYCHOACTIVE PROPERTIES OF MITRAGYNINE (KRATOM)

**Karl L.R. Jansen, M.D.***
**Colin J. Prast****

Mitragynine and several related alkaloids are derived from the leaves of *Mitragyna speciosa* (kratom), a tree that is found principally in Thailand and Malaysia. Despite their intriguing, contradictory psychoactive properties, possible medical applications and widespread use in Thailand, very little new research has appeared on these substances for over a decade (Jansen & Prast 1988).

### HISTORY

In 1836, Low noted the use of kratom by Malayans as an opium substitute (Burkill 1935), an observation that was later confirmed by Holmes (1895) who identified the leaves as those of the *M. speciosa* tree. Wray (1907b) described methods of consumption that included smoking, drinking as a tea, and chewing. The effects were said to be like opium, with large doses leading to stupor, while an "indolent life" was the consequence of habitual use (Wray 1907a). Fourteen years later, Field (1921) isolated an alkaloid from the leaves and called it mitragynine.

Burkill and Haniff (1930) noted that kratom could suppress the opiate withdrawal syndrome, reduce fever, and act as an analgesic. This inspired a series of pharmacological investigations, with experiments on animal tissues indicating that mitragynine was a central nervous system stimulant rather than a depressant (Grewal 1932a). It was said to resemble cocaine and to be used extensively in Thailand to increase work output and tolerance of intense sunlight. Habitual users were claimed to be thin, and to have dry skin and a darker complexion (Grewal 1932b). Grewal administered mitragynine to five male volunteers and confirmed that the effect was similar to cocaine.

Thuan (1957) was the first to report a case of addiction in a medical journal, presenting a chronic user who had a marked withdrawal syndrome on cessation, but who nevertheless remained in good health despite heavy use, being mentally and physically "normal." Citing Marcan (1934, 1929), Thuan maintained that kratom did not have a bad reputation like opium, nor did it cause changes in physical condition or character. The effects were once again said to resemble those of cocaine.

In the 1960's, new analytical techniques were applied to these alkaloids (Shellard 1974). Twenty-two alkaloids were isolated from *M. speciosa*, with the alkaloid content of individual trees varying according to location and season. The molecular structures were found to be indoles and oxindoles having a closed or open E ring, with substitution occurring at the C9 position (Beckett et al. 1966). Mitragynine, found only in *M. speciosa* (Shellard 1974), is the dominant alkaloid. With the methoxyl group at position 4 of the indole (see Figure 1), mitragynine appears to be analogous to the 4-substituted indole psychedelics, such as psilocybin and lysergic acid amide (Emboden 1979; Shulgin 1972; Beckett, Shellard & Tackie 1965).

The research of the 1960's and early 1970's had been funded by a quest for nonopiate analgesics. Mitragynine compared favorably with codeine as an analgesic in the dog: It did not cause emesis or dyspnea like codeine at equivalent doses, was not antagonized by nalorphine, had no opiatelike dependence syndrome, had negligible anticholinergic effects, and was much less of a respiratory

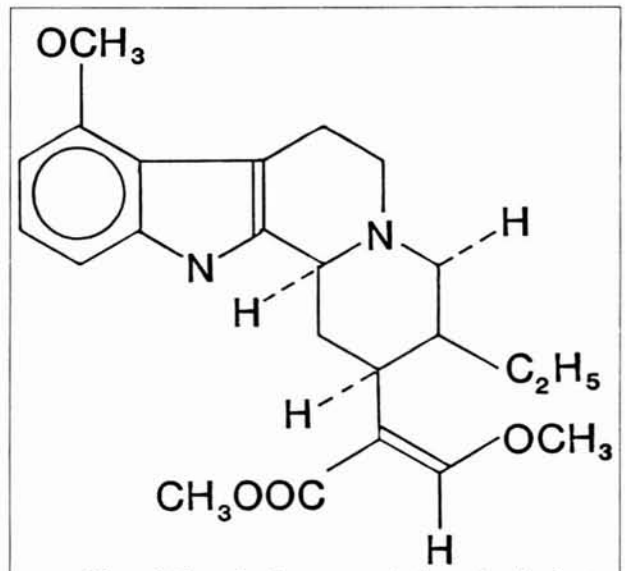


**Figure 1.** The molecular structure of mitragynine, dominant alkaloid of *M. speciosa*.

*MRC Research Fellow, Department of Anatomy and Human Biology, University of Auckland Medical School, Private Bag, Auckland, New Zealand.

**Director, Plant Medicine Research Institute, Auckland, New Zealand.

depressant. No evidence of toxicity (e.g., tremors and convulsions) was observed in mice after doses as high as 920 mg/kg. Large doses in cats had stimulating effects that were qualitatively different from those of opiates, with cats showing increased exploratory behavior without the opiate-induced "fear and rage" complex (Macko, Weisbach & Douglas 1972).

The results of a study of 30 Thai kratom users were published by Suwanlert in 1975. The sample largely consisted of older, married men who had been chronic users for over five years. In most instances, the leaves had been chewed three to 10 times a day, with stimulant effects commencing after five to 10 minutes. Key motivators were a desire to increase work output and tolerance of hot sunlight, with the drug also being said to "calm the mind."

The Thai Narcotic Book (Norakanphadung 1966) described kratom as weaker than morphine and less harmful than cocaine. It was said to have depressive effects like opium and cannabis, while also being stimulating like coca, as if chewing coca leaves and smoking opium simultaneously. Chronic consumption could cause darker skin, even if the user remained indoors. The withdrawal syndrome was said to be considerably milder than that seen with opiates. Norakanphadung described the medical use of the leaves in Thailand to replace morphine in addict detoxification and treatment programs.

## DISCUSSION

Mitragynine is thus a drug with a highly unusual but nevertheless well-documented history of being described as both a depressant and a stimulant, while at the same time possessing the chemical structure one might expect of a psychedelic. It can suppress the opiate withdrawal syndrome, but it is not reversed by nalorphine. Discovering the sites of action of this novel substance, thus resolving the apparent contradictions, may improve understanding in several areas of psychopharmacology. Just as new analytic methods were applied to the molecule in the 1960's, researchers now have at their disposal such techniques as receptor binding studies using radiolabeled compounds. Such studies have yet to be performed.

The contradictions extend to the evidence concerning side effects and the nature of risks to health from chronic use. Preclinical trials in humans, carried out by Smith, Kline and French Laboratories in the early 1970's, apparently revealed some unacceptable acute effects (Raffauf 1986). Nevertheless, kratom would seem to be well tolerated by many Asians on a daily basis. One reason for this may be the different pharmacological profiles of pure mitragynine and the unprocessed leaf, the latter containing several other substances that may modify the effects of the drug. Clinical research might be more appropriately centered on the leaves, which have been used for many years to replace opiates in addiction treatment in Thailand (Norakanphadung 1966), rather than mitragynine acetate.

Should kratom ever attain Food and Drug Administration approval, it could be valuable as an alternative to methadone. Rather than causing the patient to slow down, if given for a brief period of time it might lead to improved functioning, as it does for Thai farmers, while attenuating the opiate withdrawal syndrome.

The claim of darker skin is intriguing in combination with the psychoactive properties and molecular structure of mitragynine. Activation of the dopamine type 2 ($D_2$) receptor in the rat pituitary gland by methamphetamine attenuates the release of α-melanocyte stimulatinglike peptides (Kebabian, Beaulieu & Itoh 1984). It may be that mitragynine has an opposite effect, increasing melanocyte-stimulating substances and thus darkening the skin. If the drug proved to be a $D_2$ receptor antagonist, it might also have antipsychotic properties. Unlike some other stimulants, chronic, heavy use of mitragynine does not seem to cause paranoid disorders, although this issue has not been adequately researched.

It is thus apparent that kratom is a psychoactive drug of considerable scientific interest, even if it should never find acceptance as a clinical tool. While the latter possibility may have caused pharmaceutical companies to lose interest, much further research remains to be done, both of a pure and an applied nature. A decade is too long a period of time for no new research to have appeared on these intriguing alkaloids.

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