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Letter to the Editors

ETHNOPHARMACOLOGY OF KRATOM AND THE *MITRAGYNA* ALKALOIDS

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Sirs,

Mitragyna speciosa Korth. ("kratom", "biak") is a Southeast Asian tree, the leaves of which provide several alkaloids of considerable interest and seemingly contradictory properties. In 1836, Low (Burkill, 1935) described the use of kratom by native Malayans as an opium substitute when opium itself was unavailable or unaffordable. Holmes (1895) identified kratom as *M. speciosa* and its use as a substitute for opium was again noted. In 1907, Wray described how it may be smoked, chewed or drunk as an infusion with opium-like effects regardless of the method of administration (Wray, 1907a). Large doses were claimed to result in stupor while frequent indulgence led to an "indolent life". He expressed the hope that an active principle would soon be isolated and its usefulness to medicine assessed (Wray, 1907b). Samples of the leaves were sent to the University of Edinburgh where, 14 years later, Field (1921) isolated two new alkaloids: mitragynine (from *M. speciosa*) and mitraversine (from *M. parvifolia*). Burkill (1930) recorded the uses of kratom as wound poultice, cure for fever and suppressor of the opiate withdrawal syndrome.

The first formal pharmacological investigations were carried out at the University of Cambridge. Grewal (1932a) performed a series of experiments on animal tissues and found mitragynine to be a central nervous system stimulant rather than depressant. He wrote that in this respect it resembled cocaine and noted widespread use in Thailand to increase work efficiency, tolerance of hot sun and that addicts were claimed to be thin with distended stomachs, unhealthy complexions, dark lips and dry skin (Grewal, 1932b). Grewal subsequently administered mitragynine to five men and again observed a cocaine-like effect, discovering that in the leaf form much less alkaloid was required. Fifty milligrams of pure mitragynine acetate produced nausea and vomiting in some subjects.

The 1930s saw increasing French interest in *M. africana* (Raymond-Hamet,

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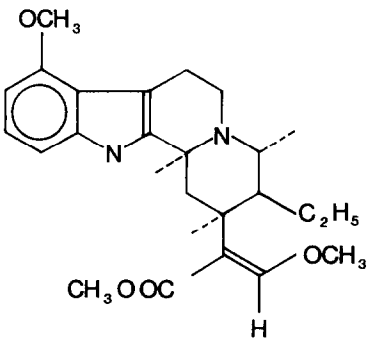

Fig. 1. Mitragynine.

1934). Further alkaloids were isolated, including mitranermine which could lower the core temperature of guinea pigs by up to 1.6°C (Perrot et al., 1936). It was hoped that the new alkaloids would replace quinine. Thuan (1957) was first to report a case of addiction in the medical literature. He presented a chronic user who had a marked withdrawal syndrome on attempted cessation, never increased his use, remained in good health, did not lose weight, and was mentally and physically "quite normal" (Thuan, 1957). Thuan quotes Marcan (1929,1934) as stating that the kratom habit does not have a bad reputation like opium smoking, nor does it cause any change in the physical condition of the addict or his character. The effects were again said to be "like cocaine" and the problem a common one in Malaya.

In the 1960s, modern analytic methods were applied to the *Mitragyna* genus alkaloids (Shellard, 1974). It soon became apparent that these were indoles and oxindoles having a closed or open E ring with substitution occuring at the C9 position (Beckett et al., 1966). Twenty-two alkaloids were isolated from *M. speciosa* alone, the exact content varying with time and location. Mitragynine (Fig. 1) is the dominant alkaloid, and exclusive to *M. speciosa* (Shellard, 1974). The methoxyl group is at position 4 of the indole, rendering mitragynine analogous to the 4-substituted indole psychedelics, e.g. psilocybin and lysergic acid amide (Beckett et al., 1965; Shulgin, 1972; Emboden, 1979).

The resurgence of interest in the 1960s had been spurred by a search for non-opiate analgesics. Macko et al. (1972) found mitragynine to be comparable with codeine as an analgesic and cough suppressant in the dog and that, unlike codeine at equivalent doses, it did not cause emesis or dyspnoea. There was no opiate-like addiction syndrome, or antagonism by nalorphine, negligible anti-cholinergic action and minimal effect on gastric motility at analgesic levels. Futhermore, it had little effect on the blood pressure of dogs, was only hypotensive in cats at high doses and was much less of a respiratory depressant than codeine. Chemically unrelated to any

known analgesic, it also appeared to be significantly less toxic. In the mouse, no evidence of toxicity (tremors and convulsions) was observed after doses as high as 920 mg/kg. Large doses in cats had stimulating effects qualitatively different from opiates; in particular, there was increased exploratory behaviour without the opiate "fear and rage" complex. Mitragynine was found to be much less active subcutaneously than orally, suggesting that the active analgesic moiety may be a metabolite (Macko et al., 1972).

Zarembo et al. (1974) produced two active metabolites using a *Helminthosporum* sp. Mitragynine pseudoindoxyl (C23, H30, N2, 05, SKF 12711-A) displayed analgesic activity in the D'Amour-Smith test almost ten-fold stronger than mitragynine when administered by both oral and intraperitoneal routes to animals. The second metabolite (C23, H30, N2, 06) was 20—30% more effective than mitragynine.

In 1975, a study of 30 Thai kratom users appeared (Suwanlert, 1975). These were mostly older, married men who had been using the drug for more than 5 years. Ninety percent chewed the fresh leaf or took it as a powder, adding salt to prevent constipation. The leaves were chewed three to ten times a day with stimulant effects beginning 5—10 min later. Almost all of the subjects said that they had become addicted because they sought to increase their work out-put. The drug was also said to "calm the mind". Side effects were listed as dry mouth, frequent micturition, constipation, small black faeces, anorexia and weight loss. The withdrawal syndrome included aggression, tearfulness, rhinoorrhea, musculo-skeletal aches and "jerky movements". The kratom habit was noted to be culture bound to the Thai and largely a ritualistic, rural phenomenon, with village society accepting male addicts who worked to support their families but not female addicts.

The so-called "Thai Narcotic Book" (Norakanphadung, 1966) stated that kratom was weaker than morphine with shorter effects, less harmful than cocaine, could cause darker skin (even if the user remained indoors) and green faeces, and had a milder withdrawal syndrome than was seen with opiates. It was said to stimulate like coca and have depressive effects like opium and cannabis, as if chewing coca leaves and smoking opium simultaneously (Norakanphadung, 1966). The book describes medical use of kratom in Thailand to replace morphine in treating addicts.

In conclusion, it appears that we are left with a drug which is claimed to be both a narcotic and a stimulant — two effects generally regarded as opposite. Even more intriguing is the connection of these effects with a chemical structure resembling a psychedelic hallucinogen rather than an opiate. It does not appear to be reversed by nalorphine and yet it is said to suppress the opiate withdrawal syndrome and to be an effective analgesic. One is left wondering at which receptor sites mitragynine might act. Resolving some of these contradictions may provide useful insights in areas of psychopharmacology. There are contradictory claims concerning its ability

to cause physical dependence, side effects, and whether long-term use is injurious to the health. Certainly the weight of evidence is insufficient to account for the paucity of further work over the past decade. Published experimental results were positive for use as analgesic, anti-tussive, and hypothermic agent in animals. It appears that pre-clinical trials in humans, carried out by Smith, Kline and French Laboratories, revealed unacceptable side-effects (Raffauf, R. (1986) pers. commun.). Nevertheless, the drug would seem to be well tolerated by a large number of Thai on a chronic basis. Future investigations may do well to concentrate upon the kratom leaves rather than pure mitragynine, as the former appears to be much better tolerated. As Chaudhury (1986) has pointed out, pharmaceutical companies entered the medicinal plant area in the 1970s and soon withdrew, sometimes failing to realise that the testing of plants already in use requires a design individually tailored for that particular plant (Chaudhury, 1986). Where such a realisation was made, F.D.A. criteria ensured that there would be little change in procedure. For example, as kratom is widely used in Thailand, detailed observations can be made of habitual users without the ethical problems of deliberate administration.

While the market now has many non-opiate analgesics, kratom may have a special role as a replacement for methadone in addiction treatment programs. If given for a brief period, it may improve functioning as observed by Thai farmers while creating a state of consciousness more favorable to psycholytic therapy. Even if kratom cannot be added to the therapeutic pharmacopeia, due to side-effects or for other reasons, the substance remains of great intrinsic scientific interest. There is a definite place for further research on kratom, at each level from folklore village use to receptor binding assays.

References

Beckett, A.H., Shellard, E.J. and Tackie, A.N. (1965) The *Mitragyna* species of Asia. Part IV: The alkaloids of the leaves of *M. speciosa* Korth. Isolation of mitragynine and speciofoline. *Planta Medica* 13, 241–245.

Beckett, A.J., Shellard, E.J., Phillipson, J.D. and Calvin, M.L. (1966) The *Mitragyna* species of Asia. Part VI: Oxindole alkaloids from the leaves of *M. speciosa* Korth. *Planta Medica* 14, 266–276.

Burkill, I.H. and Haniff, M. (1930) Malay Village Medicine. *The Gardens' Bulletin Straits Settlements* 6, 165–207.

Burkill, I.H. (1935) *A Dictionary of the Economic Products of the Malay Peninsula.* Vol II (1–2) 1966 reprint. Ministry of Agriculture and Co-operatives, Kuala Lumpur, Malaysia. p. 1508.

Chaudhury, R. (1986) Folklore herbal contraceptives and remedies. *Trends in Pharmacological Sciences* 7, 120–123.

Emboden, W. (1979) *Narcotic Plants*, Revised and Enlarged Edition, Studio Vista, London, p. 49–60.

Field, E.J. (1921) Mitragynine and mitraversine, two new alkaloids from species of *Mitragyne. Transactions of the Chemical Society* 119, 887–891.

Grewal, K.S. (1932a) Observations on the pharmacology of mitragynine. *The Journal of Pharmacology and Experimental Therapeutics* 46, 251–271.

Grewal, K.S. (1932b) The effect of mitragynine on man. *British Journal of Medical Psychology* 12, 41–58.

Holmes, E.M. (1895) Some medicinal products from the Straits settlements. *The Pharmaceutical Journal* 54, 1095–1096.

Macko, E., Weisbach, J.A. and Douglas, B. (1972) Some observations on the pharmacology of mitragynine. *Archives Internationales de Pharmacodynamie et de Therapie* 198, 145–161.

Marcan, A. (1929) Report of the Government Laboratory of Siam. *Analyst* 54, 475–479.

Marcan, A. (1934) Report of the Government Laboratory of Siam. *Analyst* 59, 753–760.

Norakanphadung Prayun (1966) *Pramuan Khuamru Ruang Yaseptit Hai Thot*, Thanyarak Hospital, Bangkok, p. 16–20.

Perrot, E.M., Raymond-Hamet, Millat L. (1936) Sur les proprietes hypothermisants de la mitrinermine. *Bulletin de l'Academie de Medecine* 116, 266–267.

Raffauf, R. (1986) Personal communication. Northeastern University, Boston.

Raymond-Hamet, Millat L. (1934) Nouvelles observations sur la mitrinermine. *Bulletin des Sciences Pharmacologiques* 41, 533–536.

Shellard, E.J. (1974) The alkaloids of *Mitragyna* with special reference to those of *M. speciosa*, Korth. *Bulletin on Narcotics* 26, 41–54.

Shulgin, A.T. (1972) Hallucinogens, CNS stimulants, and cannabis. In: S.J. Mule and H Brill (Eds.), *Chemical and Biological Aspects of Drug Dependence.* CRC Press, Cleveland, Ohio.

Suwanlert, S. (1975) A study of kratom eaters in Thailand. *Bulletin on Narcotics* 27, 21–27.

Thuan, L.C. (1957) Addiction to *Mitragyna speciosa. Proceedings of the Alumni Association, Malaya* 10, 322–324.

Wray, L. (1907a) Notes on the anti-opium remedy. *The Pharmaceutical Journal* 78, 453.

Wray, L. (1907b) "Biak": An opium substitute. *Journal of the Federated Malay States Museum* 2, 53.

Zarembo, J.E., Douglas, B., Valenta, J. and Weisback, J.A. (1974) Metabolites of mitragynine. *Journal of Pharmaceutical Sciences* 63, 1409–1415.

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