



CHAPTER I

INTRODUCTION

Mitragyna speciosa (Korth.) Havil. is a tree which grows extensively in Southeast Asia and New Guinea, known in Thai as "Gratom". The genus *Mitragyna* belongs to the subtribe *Mitragyninae* in the tribe *Cinchoneae* of the family *Rubiaceae*. This genus comprises of 10 species, all of them are trees growing in the tropical and subtropical regions of Asia and Africa. There are 6 Asian species, growing in South Asian and Southeast Asian countries, 3 West African and one East African species. Mainly arboreal in character, some species growing to a height of 30 m. *Mitragyna* species are characterized by the globular flowering head each containing up to 120 florets. Each floret is surrounded by many overlapping bracteoles which completely cover the developing florets during the flower bud stage. The inflorescence is a dichasial cyme. The fruit is a capsule containing numerous small flat seeds. The young woody shoots bear 10-12 leaves arranged in opposite and decussate pairs, each pair of leaves being accompanied by two interpetiolar stipules which initially are closely appressed and protect the apical bud. The genus was given the name *Mitragyna* by Korthals because the shape of the stigmas in the species he examined resembled

a bishop's mitre (Shellard, 1974). However, the nomenclature has frequently been confused, the genus being variously named as *Nauclea*, *Adina*, *Sarcocephalus*, and *Stephegyne* but today, according to Ridsdale's recent revision, they are recognized as follows (Ridsdale, 1978a) :-

The Asian Species :

1. *Mitragyna diversifolia* (Wall.ex G.Don) Havil.
syn : *M. javanica* Koord et Val.
2. *Mitragyna hirsuta* Havil.
3. *Mitragyna parvifolia* (Roxb.) Korth.
4. *Mitragyna rotundifolia* (Roxb.) O.Ktz.
syn : *M. brunonis* (Wall.ex G.Don) Craib
: *M. diversifolia* (auct. non Wall.ex G.Don) Havil.
5. *Mitragyna speciosa* (Korth.) Havil.
syn : *M. speciosa* Korth.
: *Nauclea speciosa* Miq.
: *Stephegyne speciosa* Korth.
6. *Mitragyna tubulosa* (Arn.) Havil.
syn : *M. tubulosa* Havil.

The West African Species :

1. *Mitragyna inermis* (Willd.) O.Ktz.
syn : *M. africana* (Willd.) Korth.
2. *Mitragyna ledermannii* (K.Krause) Ridsd.,
comb. nov.
syn : *M. ciliata* Aubr.et Pellegr.

3. *Mitragyna stipulosa* (DC.) O.Ktz.

syn : *M. macrophylla* Hiern

The East African Species :

Mitragyna rubrostipulata (K.Schum.) Havil.

syn : *M. rubrostipulacea* Havil.

: *Adina rubrostipulata* K.Schum.

Mitragyna speciosa (Korth.) Havil. is a tree of 10-25 m in height. The leaves are elliptic, 8.5-14 cm long, 5-10 cm wide (smaller at the ends of branchlets) pointed at the tip, rounded or somewhat heart-shaped at the base, and hairy on the nerves beneath. The petioles are 2-4 cm long. The flowers are crowded in round, terminal inflorescences (heads) 3-5 cm long. The calyx-tube is short and cup shaped, with rounded lobes. The corolla-tube is 5 mm long, smooth, and revolute in the margins. The fruit is oblong-ovoid and 5-7 mm long, with 10 ridges (Quisumbing, 1951).

Various parts of several species of *Mitragyna* have been used in local folklore medicine for a wide variety of diseases such as fever, colic, muscular pains, and for the expulsion of worms. The leaves of *Mitragyna speciosa* (Korth.) Havil. (known in Thai as "Gratom leaves") have long been known to possess narcotic properties and are chewed, smoked, or drunk as an infusion with opium-like effects by the native Thai and Malaysians for a long time as an opium substitute when opium itself was not procurable

and used as suppressor of the opiate withdrawal syndrome. But, in large dose it is poisonous, producing vomiting, dizziness, and stupor. In Perak of Malaysia, pounded leaves are applied to wounds and whole, heated leaves over enlarged spleens (Marcan, 1929; Burkill, 1935). In Thai folklore medicine Gratom leaves were also used for the treatment of diarrhoea.

The Gratom leaves addiction in Thailand is a very interesting phenomenon. In 1926, an extensive cultivation of Gratom in Thailand was recorded, and an increase of the marketing of the Gratom leaves (Burkill, 1935). Gratom leaves are much used for chewing by peasants, marketing gardeners, and laborers in the central and southern regions of Thailand. The addicts said that it enables them to endure great fatigue and exposure to heat in order to increase their work out-put. They can work in the rice fields, or do other manual work from morning until evening, even though it may be very hot and sunny. Addicts are, however, afraid of the rain which cause them to be chill easily. Progression to Gratom leaves addiction is a gradual process of increasing in amount and frequency of the drug consumption. In 1975, a study of 30 Thai Gratom leaves users was reported (Suwanlert, 1975). Ninety percent chewed the fresh leaves or took it as a powder, adding table salt to prevent constipation followed by large volume of water. The leaves were chewed 3-10 times a day which stimulant effects beginning 5-10 minutes

later. The user described himself as feeling happy, strong, and active. The Gratom leaves used among Thai addicts are the red midrib leaves.

In certain respects Gratom leaves addiction resembles those of drugs with narcotic properties, except that long-term Gratom leaves addicts develop a dark skin, particularly on the cheeks and lips. In the early stages of addiction the addicts can work hard and make good progress in semi-skilled and unskilled manual work. However, after prolonged addiction their energy store often drop because of physical and psychiatric disturbances. Side effects in long-term Gratom leaves addiction were listed as dry mouth, frequent micturition, constipation, small black feces, anorexia, insomnia, and weight loss. The withdrawal syndrome included aggression, tearfulness, rhinorrhoea, musculo-skeleton aches, and jerky movements (Suwanlert, 1975). Because of the harmful effects which may result from the use of Gratom leaves, the Government of Thailand passed a law (Kratom Act, B.E. 2486) which came into force on August 3, 1943 and by virtue of which it is forbidden to plant the tree, and the existing ones are to be cut down. Until now, Gratom is listed in the Schedule V under Narcotic Act, B.E.2522. Thus Gratom is still an offence in Thailand either to possess any products of this plant or to cultivate the trees. However, the measure chosen by the law to control Gratom leaves addiction has not been found to be

effective, since it is a local plant and the addiction does not have a bad reputation. The Gratom leaves habit was noted to be culture bound to the Thai and largely a ritualistic, rural phenomenon, with village society accepting male addicts who work to support their families but not the female addicts.

Phytochemical work on the alkaloids of the genus *Mitragyna* arose primarily from the narcotic properties of the leaves of *Mitragyna speciosa* (Korth.) Havil. which have been used as a drug abuse in Thailand as mentioned. The first phytochemical investigation of the alkaloids of *Mitragyna speciosa* (Korth.) Havil. was reputed to Hooper in 1907 and this was repeated in 1921 by Field who named the alkaloid mitragynine (Field, 1921). Following this quite an amount of work was carried out on species of *Mitragyna* from Africa and Southeast Asia particularly by Raymond-Hamet. In the 1960s, modern analytical methods were applied to investigate *Mitragyna* alkaloids in order to search for non-opiate analgesics (Shellard, 1974). At that time the alkaloidal content of different morphological, geographical, and chronological samples of *Mitragyna speciosa* (Korth.) Havil. have been extensively studied by research workers at Pharmacognosy Research Laboratories, Chelsea College, University of London, and 24 alkaloids have been isolated and characterized. Among those, rotundifoline, isorotundifoline, specionoxeine, and isospecionoxeine have not been obtained from materials

(mature plants) from Thailand. The variation between different batches of leaf suggest that geographical variants and even chemical races may occur in the species within Thailand while the investigation into the alkaloidal content from month to month shows that mitragynine is undoubtedly the dominant heteroyohimbine alkaloid together with speciogynine and paynantheine. The dominant oxindole alkaloids were corynoxine, mitrafoline, mitragynine oxindole B, and speciofoline. The total number of alkaloids so far isolated and characterized from the 10 species of genus *Mitragyna* exceeds 45 and in addition there are a number of alkaloid N-oxides (Shellard, Houghton and Resha, 1978b).

It is notable that most of the work previously carried out have been done using dried plant materials. This thesis describes the phytochemical investigation of the fresh leaves of *Mitragyna speciosa* (Korth.) Havil. It is undertaken in the hope that it might reveal an interesting variation in the pattern of alkaloids from those previously reported.