CHAPTER I

INTRODUCTION

Trees in the genus *Erythrophleum* Afzel. ex R. Br. (*Erythrophloeum* Afzel.) belong to the tribe Dimorphandreae, subfamily Caesalpinoideae, of the family Leguminosae (Dalma, 1954; Jackson, 1893; Prain, 1913). These plants are found in Africa, Asia and Australia (Cronlund, 1973 a). In Asia, they are widely distributed in Southern China, Indo-China, Thailand, Borneo and the Philippines (Burkill, 1935). According to the Index Kewensis and its supplements, the genus consists of 20 species as follows:

1. *Erythrophleum africanum* Harms (*Gleditschia africana* Benth.)
2. *E. angustifolium* Gagnep.
3. *E. cambodianum* Gagnep. (*Albizzia cambodiana* Pierre)
4. *E. chlorostachys* Baill. (*E. chlorostachys* Hennings, *E. laboucherii* F. Muell)
5. *E. couminga* Baill.
6. *E. densiflorum* Merrill (*Cynometra densiflora* Elm.)
7. *E. dinklagei* Taub. (*Calpocalyx dinklagei* Harms)
8. *E. fillaea* Guill. & Perr.
9. *E. fordii* Olivier
10. *E. gabunense* Taub.
11. *E. guineense* G. Don (*E. judiciale* Procter, *E. ordale* Bolle, *E. suaveolens* (Guill. & Perr.) Brenan, *Fillaea suaveolens* Guill. & Perr.)
12. *E. ivorense* A. Chev. (*E. micranthum* Harms)
13. *E. lasianthum* Crobishley
14. *E. le-testui* A. Chev.

15. *Erythrophleum mavia* Bertol

16. *E. pubistamineum* Hennings

17. *E. purpurascens* A. Chev. (*Piptadenia chevalieri* Harms)

18. *E. succirubrum* Gagnep.

19. *E. teysmannii* Craib (*Albizzia teysmannii* Kurz.)

20. *E. unijugum* Airy-Shaw

(Duran and Jackson, 1901-1905; Hill, 1926; Hill, 1929; Hill, 1933; Jackson, 1893; Prain, 1913; Prain, 1921; Salisbury, 1947; Taylor, 1959; Taylor, 1966; Thiselton-Dryer, 1904).

The only two species of *Erythrophleum* which grow wild in the deciduous forest of north-eastern, eastern, central and the upper part of southern of Thailand, are *Erythrophleum succirubrum* Gagnep. (Saat, "ซาด"; Phansaat, "พันซาด"), *E. teysmannii* Craib (Saak, "ซาก"; Tra, "ตะ") and *E. teysmannii* Craib *var. puberulum* Craib (Khraak, "คราก"; Tria, "เตรีย"; Phansaat, "พันซาด") (Smitinand, 1980). These two species, having very similar characters, are large trees with cylindrical erect trunks about 11 meters in height, 0.8-1.0 meter in diameter. The light brown heartwood is very hard, not affected by termites and used as structural timber. The leaves are bipinnately compound leaf, petiole 17-20 cm long, with 2-4 pairs opposite petiolets for 10-30 cm of their length. There are 10-16 alternate sessile leaflets in each petiolet. The leaflet is ovate or elliptic, pubescent, except that of *E. teysmannii* Craib, 4-8 cm long by 2.5-5 cm wide. The inflorescences are axillary or terminal raceme, 5-10 cm long, with small yellow flowers. The fruits are flat legume like that of *Albizia lebbeck* (L.) Benth., dehiscent, 12-18 cm long by 25-30 mm wide, 5-8 seeds. The black brown seeds are hard obovule, 12-14 mm long by 7-9 mm wide (Lecomte, 1908-1923). The leaflet base of

*Erythrophleum teysmannii* Craib *var. puberulum* Craib is not cordate but that of *E. succirubrum* Gagnep. is (Craib, 1931).

In Thailand the heartwood of *Erythrophleum* is burnt for high heat charcoal called Tan-tum-tong, "ถ่านทำทอง" which is used as an antipyretic. All parts of these plants such as leaves, wood, bark, root and seeds are very toxic and have caused death (Pongboonrod, 1971). In Krasang district, Buriram province, one of the four ten-year-old children died after taking the seeds and the others who took about 2-3 seeds have been alive with the symptoms of dyspnea, arrhythmia, myosis and unconsciousness.

In East Africa *E. africanum* Harms is regarded as poisonous. The root yields poisonous alkaloids and the leaves are recorded as highly toxic to livestock. The tree is reported to have been used as an ordeal tree (Watt, 1962). The bark decoction has been prescribed against toothache (Jansson and Cronlund, 1976).

*E. chlorostachys* (F. Muell) Baill., commonly known as Ironwood, is a large tree endemic in Australia. All parts of the tree are extremely poisonous and large numbers of sheep and cattle died from eating the leaves. Two leaves are reputed to be sufficient to kill a goat (Griffin *et al.*, 1971).

*E. couminga* Baill., common in Madagascar and the Seychelles islands, is more toxic than *E. guineense* G. Don, and the leaves have been the cause of mass poisoning of livestock (Dalma, 1954).

*E. densiflorum* Merr., in the Philippines and Malaysia, is devoid of toxic alkaloids but *E. fordii* Oliv., in Southern China and Indo-China, seems to contain poison in its bark (Burkill, 1935).

*Erythrophleum guineense* G. Don is known as the Ordeal tree or Red Water tree in Africa, according to the used of bark to prepare an intensely colored infusion (Dalma, 1954). The highly poisonous bark has been used by the African as an arrow poison, as a fish poison and as a poison for trial by ordeal. In Tanganyika a weak maceration or a decoction of the bark is used as an anthelmintic and the leaves as a snake-bite remedy. The Congo Africans use the powdered bark as an antidote to injurous medicines and as a protection against injurous magic. The Zulus use the powered bark for the relief of headache and cold by their sternutatory action. In the Cameroon the bark is used as an emetic and purgative, in Sierra Leone for rheumatism, in West Africa for skin diseases, in French Guinea as a purgative. In parts of West Africa, the bark is used to kill rat and to poison water where game animals drink, while the leaves are placed in corn to keep insects away (Watt, 1962).

The bark and seeds of *E. lasianthum* Crob. are used medicinally by the Zulus, who have been known to use the bark for murder. The powdered bark is used as a snuff for the relief of headache and internally for abdominal complaints and to cure abortion in the dog. For these purposes the seeds may be used instead of the bark but it is said to be more powerful in its action. Sheep, fed on the plant for few days, develope a diarrhoea which proves fatal after a week. The bean given about 0.5 g by the mouth to a rabbit, produces cardiac symptoms in 45 minutes and death within an hour (Watt, 1962).

The *Erythrophleum* alkaloids are usually isolated from bark extracts. Chemically the alkaloids are built up of a diterpenic acid, or in few cases cinnamic acid, which is esterified or, eventually, amide

bounded to a secondary or tertiary aminoethanol (Cronlund, 1973 a). These alkaloids have an intense action as a cardiac stimulant which is quite like that produced by the digitalis glycosides. Both of these drugs suffer from the disadvantage of producing toxic symptoms in doses only slightly higher than those producing therapeutic effects (Clarke *et al.*, 1967 a, b).

Chen and his associates studied the relative potencies of erythrophleine, coumingine, coumingaine, cassaidine, homophleine, cassaine and acetylcassaine and concluded that coumingine was the most potent cardiac stimulant, its effect being about equal to that of scillaren A (Dalma, 1954). Mailing and Krayer have found norcassaidine to be the most potent of the *Erythrophleum* alkaloids, cassaine half as potent and erythrophleine one-fourth as potent. Cotten *et al.* reported that cassaine and cassaidine are both quantitatively more active than ouabain (Watt, 1962). Cronlund (1973 a) reported that coumidine has almost the same potency as ouabain and ivorine is more potent than N-methyl derivative of ivorine, since monoethylamino esters in general are more potent than dimethyl analogs.

Santi and Zweifel determined the minimum lethal dose for cassaidine, cassaine, homophleine, erythrophleine and coumingine by injection into the ventral sack of the frog and by subcutaneous injection into white mice. The toxicity increased in the order given, and coumingine showed observable responses on the isolated frog heart at a dilution of 1 to 5 million (Dalma, 1954). Clarke *et al.* (1967 a) showed that low concentration of cassaine possesses positive inotropic activity in the isolated appendage of the rabbit heart. As the concentration increased, toxic effects were observed, i.e. arrhythmic beating, a negative

inotropic action and cessation of beating. A similar sequence of effects was observed after injecting single dose of cassaine to the intact anesthetized dog. Low dose produced an increase in ventricular contractile force, intermediate dose resulted in cardiac slowing and high dose evoked toxic effects, i.e. A-V block, ventricular ectopic beats, ventricular fibrillation and respiratory arrest.

Dalma (1954) concluded the poisonous effects of these alkaloids as follows:

... typical digitalis-like cardiac action, paralysis of the respiratory center, strong adrenaline-like blood pressure increase, emetic action, diarrhea with bloody stools, strong salivation, dyspnoea, uncertainty of movements, trembling of the extremities, thirst, headache, visual and general sensual disturbance, and depressing action on the cortex (except cassaine which has an exciting action) with temporary periods of excitation accompanied by tonic and clonic cramps. Death is dued to cardiac and respiratory paralysis. The alkaloids also induce intense and long-lasting local anesthesia accompanied in most cases by irritation of the tissues concerned.

Loder *et al.* (1974) have found that the bark extract from *Erythrophleum chlorostachys* Baill. shows significant cytotoxicity against cells derived from human carcinoma of the nasopharynx carried in cell culture (KB). Subsequent fractionation of this material traced high cytotoxicity to the alkaloids ($ED_{50}$ 0.02 µg/ml). In 1975, Loder and Nearn isolated the alkaloids and reported that the alkaloids show high cytotoxicity against the KB cell culture as follows: 3β-acetoxy-norerythrosuamine ($ED_{50}$ 0.0003 µg/ml), 3β-acetoxynorerythrostachaldine HCl ($ED_{50}$ 0.0073 µg/ml), norerythrostachaldine HCl ($ED_{50}$ 0.029 µg/ml). They also reported the amide alkaloids are much less active against the KB cell culture and have the following $ED_{50}$ values (µg/ml): norerythro-stachaldide 2.1; 3β-acetoxynorerythrostachaldide 2.6; norcassamide 29;

norcassaidide 31, 18; norerythrophlamide > 100; norerythrostachamide > 100 (Loder *et al.*, 1974; Loder and Nearn, 1975 b).

Up to the present time, there are only six species of the genus *Erythrophleum* which have been studied for their alkaloidal contents, especially of the bark. The two species in Thailand which are recorded as poisonous plants have never been studied chemically. For the thesis project, the author selects *Erythrophleum teysmannii* Craib *var. puberulum* Craib, one of these species, to investigate the alkaloidal constituents of its bark and hopes that this investigation will reveal the characteristics of its alkaloids and stimulate the pharmacologists to study their pharmacological effects.