

The plant contains a *bis*-benzylisoquinoline known as phaeantharine which has shown some potential as an insecticidal agent and exhibited some levels of antibacterial activity.^{3,4} It would be interesting to learn whether this plant has any neuropharmacological potential.

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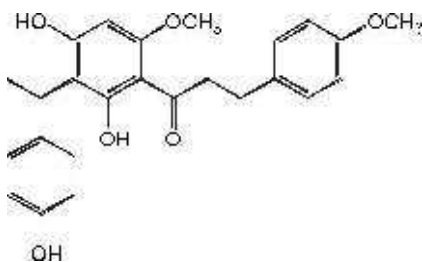
CHAPTER 3 Medicinal Plants Classified in the

3.1 GENERAL CONCEPT

The family Myristicaceae (R. Brown, 1810 nom. conserv., the Nutmeg Family) consists of approximately 16 genera and 380 species of tropical rain forest trees, which are in field collection, recognized easily by making a cut in the bark from which will exude a blood-like sap. Myristicaceae have attracted a great deal of interest since they produce indole alkaloids, which might hold potential for the treatment of depression and other central nervous system (CNS) diseases. *N,N*-dimethyl tryptamine, 5-methoxy-*N,N*-dimethyl tryptamine, 2methyl-1,2,3,4-tetrahydro- β -carboline have been identified with *Virola sebifera*, which is used by South American shamans to cause hallucination (Figure 3.1). Other interesting principles from Myristicaceae are phenylacylphenols and phenylpropanoids. Examples of phenolic compounds of pharmacological value in Myristicaceae are kneracheline A and B, from *Knema furfuracea*, which inhibit the proliferation of bacteria cultured *in vitro*; also 3-undecylphenol and 3-(8*Z*-tridecenyl)-phenol from *Knema hookeriana*, which inhibit the proliferation of *Bursaphelenchus xylophilus* cultured *in vitro* with a maximum effective dose of 4.5mg/cotton ball and 20mg/cotton ball, respectively.^{1,2}

Note that phenolic compounds from the stem bark of *Knema glomerata* inhibit moderately the proliferation of human tumor cell lines cultured *in vitro*.³ Phenylpropanoids are centrally active and myricetin and elemicin from nutmeg (*Myristica fragrans* Houtt.) are narcotic. In the Pacific Rim, approximately 20 species of plants classified within the family Myristicaceae are medicinal.

Family Myristicaceae



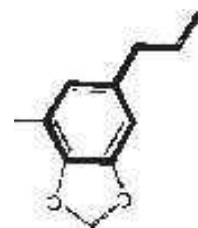
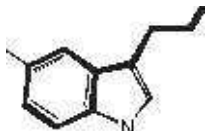
Iryantherin A

H3CO OO

Myristicin

CH₃ N CH₃

HO



H

5-Hydroxy-N,N-dimethyl tryptamine

Figure 3.1 Examples of bioactive natural products from the family Myristicaceae.

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Figure 3.2 *Knema glaucescens* Jack. [From: Flora of Borneo. Bukit Raya Expedition. Veldkamp No: 8522.

Feb. 4, 1984. Geographical localization: Borneo, Batu Bading, KCT, 47Km, 113°50' E, 1°15' S.

96Km, in primary dipterocarp forest.]

3.2 KNEMA GLAUCESCENS JACK

[From: Greek *knema* = internode and *glaucescens* = somewhat glaucous.]

3.2.1 Botany

Knema glaucescens Jack (*Knema palembanica* Warb.) is a tree that grows in the rain forest of Indonesia and Borneo to a height of 15m. The bark exudes a red sap after being incised. The stems are 4mm in diameter with a velvety apex. The leaves are simple, spiral, and exstipulate. The petiole is 7mm × 2mm, and velvety. The blade is lanceolate, shows 22 pairs of secondary nerves, and is 11.3cm

× 3.2cm – 12.8cm × 2.6cm – 13.3cm × 3.6cm – 13cm × 3.2cm. The midrib is velvety above and the blade is glaucous below. The fruits are ovoid, and are 2.2cm × 1.7cm on an 8mm pedicel (Figure 3.2).

3.2.2 Ethnopharmacology

The plant is called *Kumpang* by the Iban tribes of Sarawak where a decoction of bark is used to treat abdominal discomforts. The pharmacological properties are unexplored. Are serotonin-like principles present here?

3.3 *KNEMA GLOBULARIA* (LAMK.) WARB.

[From: Greek *knema* = internode and Latin *globulus* = globe.]

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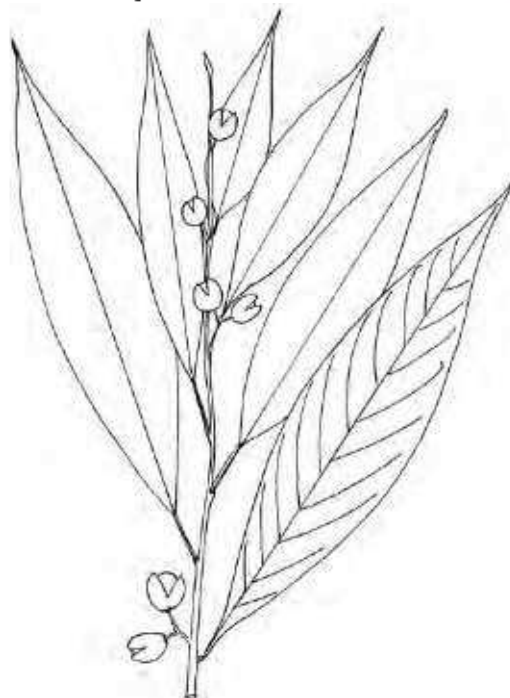


Figure 3.3 *Knema globularia* (Lamk.) Warb. [From: Distributed from the Botanic Gardens Singapore. Geographical localization: Duchong Island, Pahang. Sea level. Aug. 22, 1935. Botanical identification:

J. Sinclair, Nov. 5, 1963. Field collector: E. J. Corner.]

3.3.1 Botany

Knema globularia (Lamk.) Warb. (*Myristica globularia* Lamk., *Myristica lanceolata* Wall., *Knema corticosa* Lour., *Knema corticosa* Lour. var. *tonkinensis* Warb., *Knema missionis* [Wall.] Warb., *Knema petelotii* Merr., *Knema sphaerula* [Hook. f.] Airy Shaw, *Knema wangii* Hu, *Myristica corticosa* [Lour.] Hook. et Thoms., *Myristica glaucescens* Hook., *Myristica sphaerula* Hook., and *Myristica missionis* Wall. ex King) is a tree that grows to a height of 15m with a girth of 25cm in the primary rain forests of China and Southeast Asia. The bark is grayish-brown, and exudes a red sap after incision. The stems are rusty tomentose at the apex. The leaves are simple, exstipulate, and spiral. The petiole is 1.5cm long. The blade is thin, oblong, lanceolate, 16cm × 3.9cm – 11cm × 2cm. The apex is acute or acuminate, the base is broadly cuneate to suborbicular, and shows 19 pairs of secondary nerves. The fruits are globose and yellow, 1.3cm × 1.2cm. The seeds are solitary and enveloped in a red aril (Figure 3.3).

3.3.2 Ethnopharmacology

The plant is known as Seashore Nutmeg, Small-Leaved Nutmeg, and *xiao ye hong guang shu* (Chinese). In Cambodia, Laos, and Vietnam, the seeds are used as an ingredient for an external preparation used to treat scabies. The therapeutic potential of *Knema globularia* (Lamk.) Warb. is unexplored. Knerachelimes with antibacterial potential are elaborated by this plant.

3.4 MYRISTICA ARGENTEA WARB.

[From: Greek *muron* = a sweet juice distilled from plants and Latin *argentea* = silvery.]

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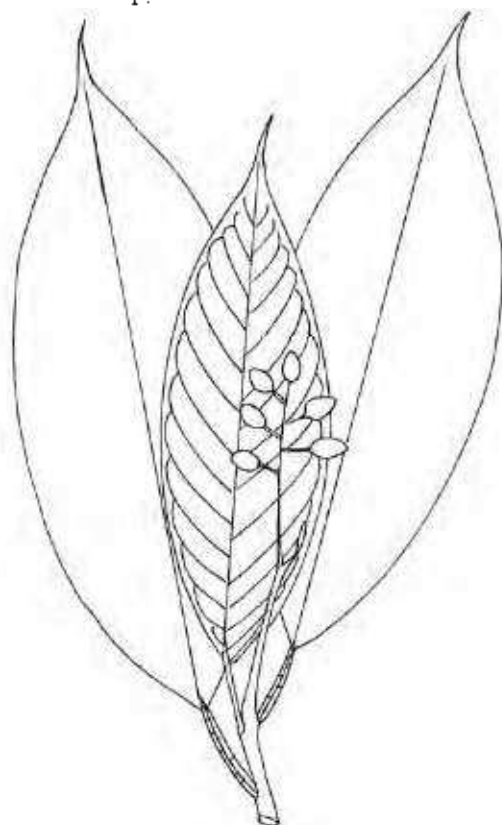


Figure 3.4 *Myristica argentea* Warb. [From: BOSWESSEN. Nederlands Nieuw-Guineë. Forestry Division Neth. New Guinea]. Field collector: C. Kalkman. No: B/W/ 6346. June 21, 1959. Botanical identification:

J. Sinclair. Nov. 13, 1962. Geographical localization: Nederland's New Guinea, Fak-Fak, Agricultural Exp. Gard. Alt.: 75m.]

3.4.1 Botany

Myristica argentea Warb. is a tree that grows in the primary rain forests of Papua New Guinea. The leaves are simple and spiral. The petiole is stout, cracked transversally, channeled, and 2.8cm long. The blade is glossy, 20cm × 6.4cm – 13.5cm × 5.6cm – 19cm × 6cm, elliptic, acuminate at the apex in a tail, and shows 13–18 pairs of secondary nerves. The inflorescences are 4.5cm-long racemes. The fruits are globose and 6mm long (Figure 3.4).

3.4.2 Ethnopharmacology

The plant is known as Macassar mace, female nutmeg, horse nutmeg, long nutmeg, Macassar nutmeg, New Guinea nutmeg, Papua mace, and Papua nutmeg. The fruits are used to treat diarrhea and to stimulate venereal appetite in Indonesia where it is called *pala negri*, *pala papoes*. The mace *Myristica argentea* Warb. abounds with a series of diaryldimethylbutane lignans of possible pharmacological value. Such lignans are erythro-austrobailignan-6 and meso-dihydroguaiaretic acid,

myristargenol A, and myristargenol B from the aril of the seeds, and show some levels of activity against

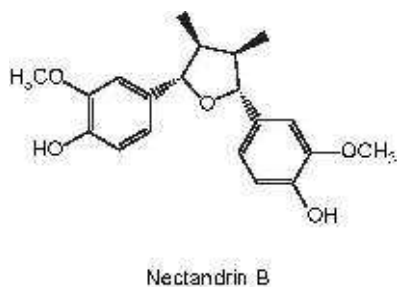


Figure 3.5

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Streptococcus mutans.^{4,5}

Erythro-austrobailignan-6, meso-dihydroguaiaretic acid, and nectandrin-B exert an antiproliferative effect on MCF-7 cells as well as antioxidant activity on the 1,1-diphenyl-2-picrylhydrazyl (DPPH) radical. In addition, Nectandrin-B (Figure 3.5) inhibits the enzymatic activity of 17 β hydroxysteroid dehydrogenase and antiaromatase activities.⁶ Is the aphrodisiac property of the fruit linked to hormonal mechanisms?

3.5 MYRISTICA ELLIPTICA WALL. EX HOOK. F. THOMS.

[From: Greek *muron* = a sweet juice distilled from plants and Latin *elliptica* = elliptical, about twice as long as wide.]

3.5.1 Botany

Myristica elliptica Wall. ex Hook. f. Thoms. (*Myristica elliptica* var. *elliptica* J. Sinclair) is a large buttressed tree that grows to 10m in the primary rain forest of Southeast Asia in rain forest swamps and riverbanks. The bark exudes a sticky red sap after incision. The leaves are simple and exstipulate. The petiole is fissured, 2cm long, and channeled above. The blade is elliptic, 17cm \times 6cm – 16cm \times 5cm and shows 7–12 pairs of secondary nerves. The fruits are conspicuous, and up to 7cm \times 5cm and attached to a 4mm-diameter pedicel (Figure 3.6).

3.5.2 Ethnopharmacology

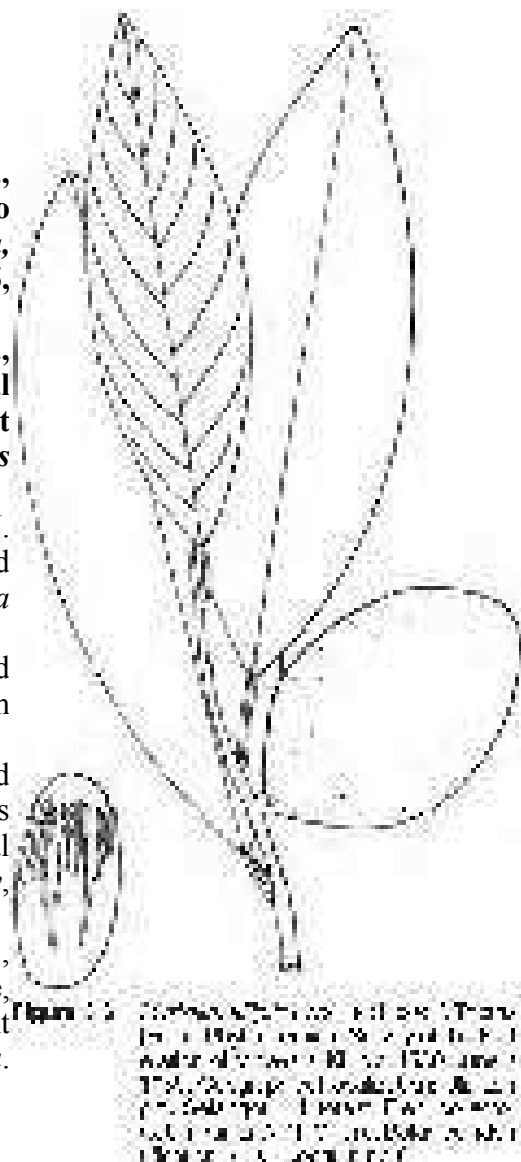
In the Philippines, the seeds or a paste of bark is applied to itchy parts of the body. In Malaysia, the fruit is known as *buah penarahan* and known to be stupefying. The pharmacological potential of this plant is to date unexplored. One may, however, set the hypothesis that the stupefying property is owed to a series of phenylpropanoids.

Figure 3.6 *Myristica elliptica* Wall. ex Hook. f. Thoms. [From: *Phytochemical Survey of the Federation of Malaysia*. KL No: 1530. June 3, 1959. Geographical localization: Ulu Langat, Selangor. Hill forest. Field collector:

G. Umbai for A. N. Millard. Botanical identification: K. M. Kochummen]

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CHAPTER 4

Medicinal Plants Classified in the Family Lauraceae

4.1 GENERAL CONCEPT

The family Lauraceae (A. L. de Jussieu, 1789 nom. conserv., the Laurel Family) consists of 50 genera and 2000 species of trees and shrubs which are recognized in field collection by their aroma, the bark which is smooth and thick, the bay-like leaves, and their drupaceous fruits which are glossy and ovoid seated on a cupular vestigial perianth. *Laurus nobilis* L. (Sweet Bay Laurel, *Lauri fructus*; *Swiss Pharmacopoeia* 1934), *Cinnamomum zeylanicum* Nees (cinnamon), *Cinnamomum camphora* (L.) T. Nees & Eberm. (camphor), *Persea americana* Miller (avocado), *Sassafras albidum* (Nutt.) Nees (sassafras oil), *Umbellularia californica* (California Bay Laurel), *Persea nanmu* Oliv. (*nan-mu* wood), *Nectandra rodiaei* Schk. (green, heartwood), *Eusideroxylon zwageri* (ironwood), and *Ocotea bullata*

E. Mey. are classical examples of Lauraceae. This family is interesting because the alkaloids it produces are cytotoxic and neuroactive (Figure 4.1). In the Asia-Pacific, there are approximately 150 species of plants classified within the family Lauraceae among which are *Cinnamomum sintoc*,

Beilschmiedia pahangensis, *Beilschmiedia tonkinensis* Ridl., *Cryptocarya griffithiana*, *Litsea cubeba*, *Litsea odorifera*, and *Litsea umbellata*, which are discussed in this chapter.

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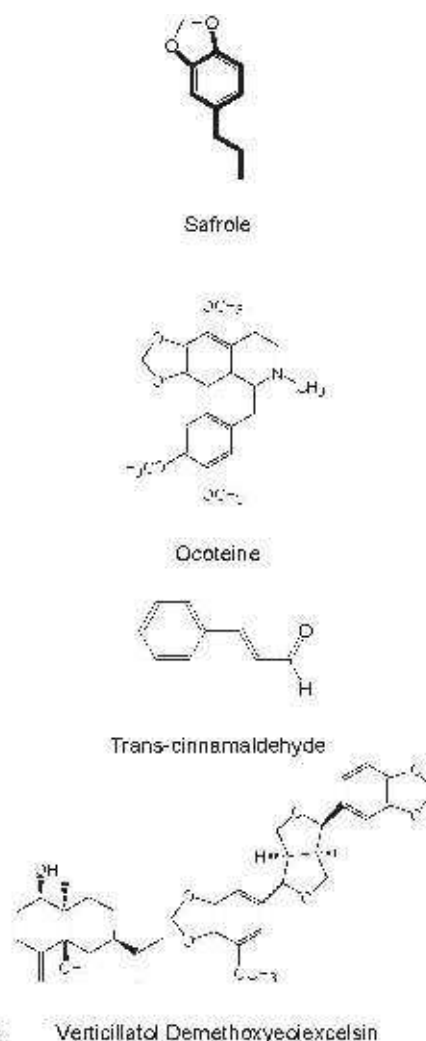


Figure 4.1 Examples of bioactive natural products characteristic of the family Lauraceae.

4.2 CINNAMOMUM SINTOC BL.

[From: Greek *kinnamon* = cinnamon and Javanese *sintok* = vernacular name of *Cinnamomum sintoc* Bl.]

4.2.1 Botany

Cinnamomum sintoc Bl. (*Cinnamomum cinnereum* Gamb.) is a tall tree which grows to a height of 40m with a girth of 2.5m. The plant is quite common on the hill forests of Thailand, Indonesia, and Malaysia. The bark is gray-brown, smooth to shallow fissured. The inner bark is reddish with a strong aromatic smell. The sapwood is pale whitish. The leaves are simple, exstipulate, and subopposite. The petiole is 0.8–1.8cm long. The blade is leathery, ovate, lanceolate, 7cm – 22cm × 3cm – 8.5cm, and blunt at the apex. The margin of the leaves is characteristically wavy. The blade shows 3–4 pairs of secondary nerves. The inflorescences are axillary panicles that are up to 15cm long. The flowers are white to pale yel-



Figure 4.2 *Cinnamomum sintoc* Bl. [From: July 28, 1998. Field collector: F. Mohd. Geographical localization: Larut Hill, Taiping. Alt.: 500m. FRI No: 42 939. Botanical identification: A. S. Mat.]

Figure 4.2 *Cinnamomum sintoc* Bl. [From: July 28, 1998. Field collector: F. Mohd. Geographical localization: Larut Hill, Taiping. Alt.: 500m. FRI No: 42 939. Botanical identification: A. S. Mat.]

seated on a cup-shaped entire rimmed perianth

500m. FRI No: 42 939. Botanical identification: A. S. Mat.]

(Figure 4.2).

identification: A. S. Mat.]

4.2.2 Ethnopharmacology

The plant is an esteemed remedy for chronic diarrhea and as an antispasmodic by the natives of the Malay coast of New Guinea where it is known as *sintok*. The pharmacological potential of *Cinnamomum iners* Reinw. ex Bl. would be worth studying, as interesting findings have been made in other *Cinnamomum* species such as the antidiabetic effect of *Cinnamomum cassia* and *Cinnamomum zeylanicum* *in vivo* and *in vitro*.¹

4.3 BEILSCHMIEDIA PAHANGENSIS GAMB.

[After K. T. Beilschmied (1793–1848), pharmacist, and from Latin *Pahangensis* = from Pahang.]

4.3.1 Botany

Beilschmiedia pahangensis Gamb. is a tree which grows to a height of 15m and a girth of 90cm. The plant is quite common along the riverbanks in primary rain forests of South Thailand, Pahang, Kelantan, and Perak. The stems are slender and slightly flattened. The leaves are simple, alternate, and exstipulate. The petiole is 0.5–1cm long. The blade is elliptic to lanceolate, 7cm – 15cm × 2cm – 5.5 cm. The apex is blunt and the base is cuneate. The blade shows 5–10 pairs of secondary nerves. The flowers are arranged in axillary panicles. The fruits are ellipsoid-oblong, 3.5cm × 1.3cm, with a blunt apex and base (Figure 4.3).

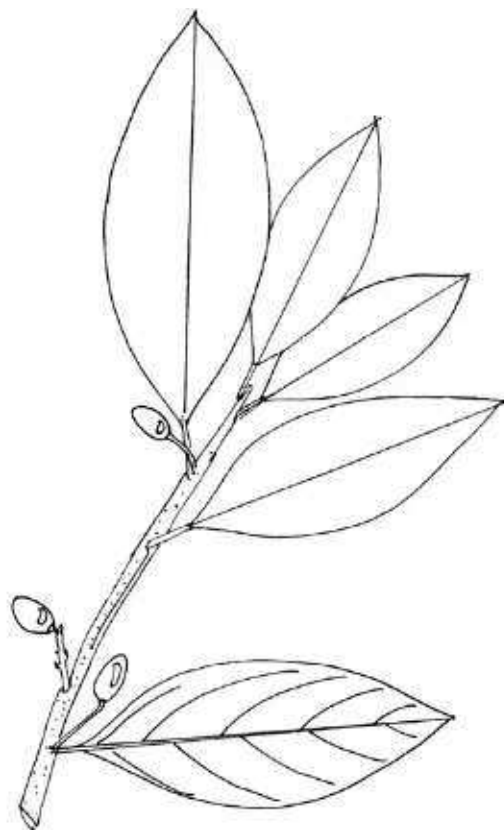


Figure 4.3 *Beilschmiedia pahangensis* Camb. [From: Flora of Malaya. Comm. Fl. Herb. Hort. Bot. Sing. Field collector: M. Shah. No. No: 2040. Geographical localization: Jeram Panjang, Pahang.]

4.3.2 Ethnopharmacology

In Peninsular Malaysia, a decoction of bark is used as a drink as a protective remedy after childbirth; it is also used to assuage stomach pains and to treat diarrhea. To date the pharmacological potential of this plant is unknown. Dehatrine *bis*-benzylisoquinoline alkaloid from the Indonesian medicinal plant, *Beilschmiedia madang* Bl. inhibits the survival of *Plasmodium falciparum* K1 strain (chloroquine resistant) cultured *in vitro* with similar activity to quinine.²

4.4 *BEILSCHMIEDIA TONKINENSIS* RIDL.

[After K. T. Bielschmied (1793–1848), pharmacist, and from Latin *tonkinensis* = from Tonkin in Indochina.]

4.4.1 Botany

Beilschmiedia tonkinensis Ridl. is a tree which grows to a height of 15m and a girth of 120cm in the rain forests of Vietnam, Cambodia, Laos, Thailand, and Malaysia. The stems are pale whitish. The leaves are aromatic, simple, alternate, and exstipulate. The petiole is 1–1.25cm long. The blade is leathery, elliptic, 7cm – 18cm × 3cm – 6cm. The apex is blunt and the base is cuneate. The blade

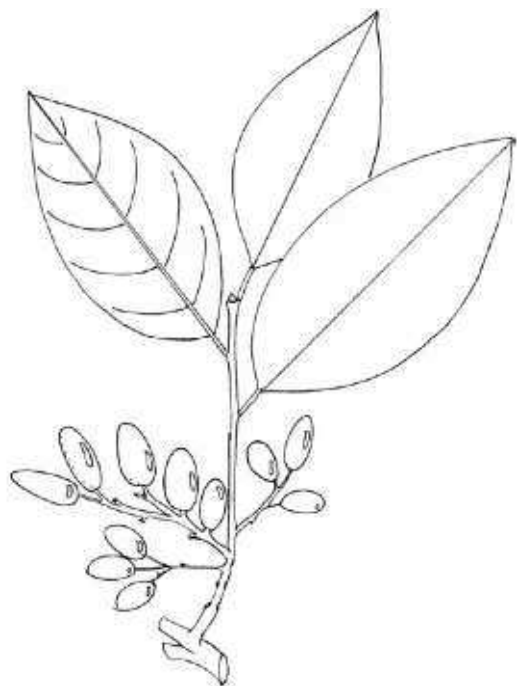


Figure 4.4 *Boisschniadia tonkinensis* Ridl. [From: Flora of Malay Peninsula. Forest Department. Geographical localization: Kuala Rompin, Pahang, April 8, 1921. No: 4181. Botanical identification:

I. H. Burkill.]

shows 6–9 pairs of secondary nerves, as well as tertiary nerves. The flowers are hairy and arranged in axillary panicles. The fruits are oblong, 2.5cm × 1.5cm with a slender 1cm-long stalk (Figure 4.4).

4.4.2 Ethnopharmacology

The leaves of the plant are used by Indonesians and Malays, who call it *medang pungok* or *medang serai*, to make poultices for application to broken bones. The pharmacology is unexplored.

4.5 CRYPTOCARYA GRIFFITHIANA WIGHT

[From: Greek *kryptos* = hidden and *karyon* = nut, and after W. Griffith (1810–1845), doctor and botanist of the East India Company.]

4.5.1 Botany

Cryptocarya griffithiana Wight is a tree that grows to a height of 20m and is 125cm in girth. The plant grows wild in the primary rain forests of Burma, Thailand, Malaysia, Indonesia, Borneo, and the Philippines. The bole is brownish and scaly. The inner bark is reddish-brown and granular. The sapwood is pale yellow. The stems are stout and covered with reddish-brown velvety hairs. The leaves are simple, exstipulate, and leathery. The petiole is 0.7–2.5cm long and velvety. The blade is elliptic to oblong, 12cm – 32cm × 8cm – 15cm. The upper surface is glabrous except for the midrib. The blade shows 5–8 pairs of secondary nerves. The lower surface is glaucous and densely velvety. The apex is rounded and the base is asymmetrical. The flowers are arranged in terminal and axillary reddish panicles. The fruits are greenish, oblong to ovate, and 2.5cm × 1.5cm (Figure 4.5).

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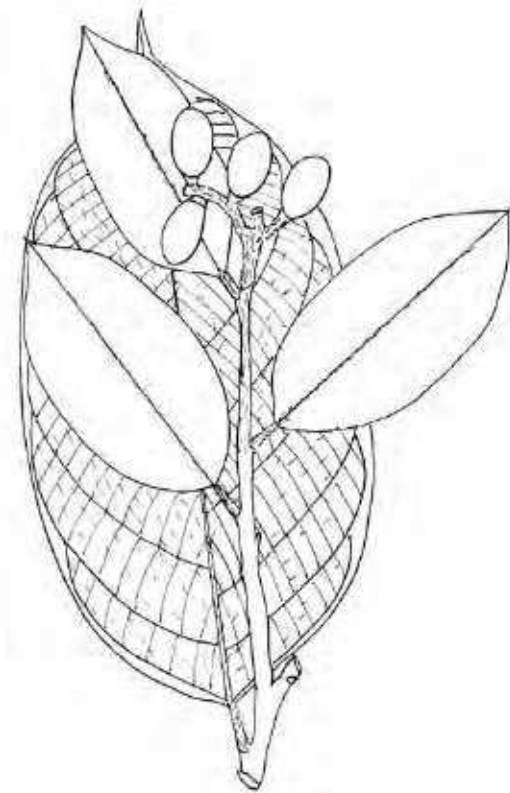


Figure 4.5 *Cryptocarya griffithiana* Wight. [From: Flora of Malaya, No. 13611. Geographical localization: Central Pahang, Tapah Hill, South Boundary Krau Game Reserve, Nov. 9, 1969. B. Everett.]

4.5.2 Ethnopharmacology

The plant is not medicinal but has the reputation in Southeast Asia for being poisonous. African medicinal plants *Cryptocarya latifolia* Sonder, *Cryptocarya myrtifolia* Stapf., *Cryptocarya transvaalensis* Burt Davy, *Cryptocarya woodii* Engl., and *Cryptocarya wyliei* Stapf, inhibit *in vitro* the enzymatic activity of COX-1 and COX-2.³ What about *Cryptocarya griffithiana* and Southeast Asian congeners?

4.6 CRYPTOCARYA TOMENTOSA BL.

[From: Greek *kryptos* = hidden and *karyon* = nut, and from Latin *tomentosa* = densely covered with matted wool or short hair.]

4.6.1 Botany

Cryptocarya tomentosa Bl. is a medium-sized tree that grows to a height of 20m with a girth of 105cm in the primary rain forests of Thailand, Malaysia, Borneo, and Indonesia. It grows to a height of 1000m in lowland to upper hill forests. The bark is reddish and finely scaly. The bole is buttressed. The inner bark is deep yellow, turning brown on exposure. The petiole is 0.5–1.5cm long, and finely hairy. The blade is elliptic, to oblong, to lanceolate, and 9.5cm – 20cm × 4cm

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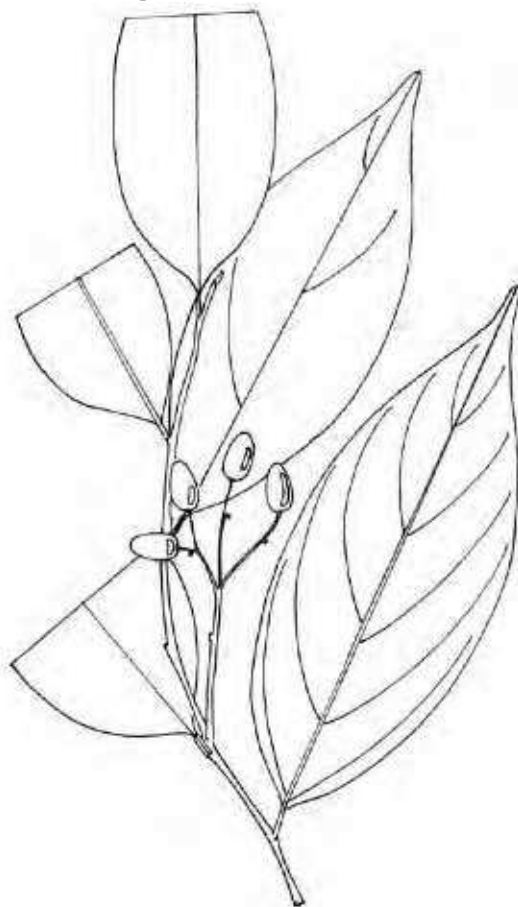
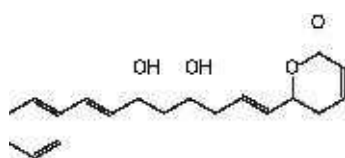


Figure 4.6 *Cryptocarya tomentosa* Bl. [From: Flora of Malaya. FRI No: 11592. Geographical localization: Lesong Botanical identification: F. S. P. Ng, Feb. 27, 2004.]

– 9cm. The apex has a pointed base that is cuneate, and the lower surface is faintly glaucous and finely hairy. The midrib is sunken above and there are 6–8 pairs of secondary nerves. The tertiary nerves are scalariform. The fruits are ellipsoid, 2.8cm × 1.5cm, fleshy, and very black (Figure 4.6).

4.6.2 Ethnopharmacology



Cryptofolione

Figure 4.7

The bark of *Cryptocarya* has the reputation in Southeast Asia of being poisonous, probably due to substances of an isoquinoline-like nature. Note that *Cryptocarya* are interesting for the pyrone they elaborate, such as cryptofolione (Figure 4.7) and one might look into their potential as a source of anxiolytic agents⁴ since cryptofolione has some chemical similitude with Kawain, the principle of kava (Piperaceae).

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4.7 LITSEA UMBELLATA (LOUR.) MERR.

[From: Chinese *litse* = *Litsea* and from Latin *umbellata* = refers to the arrangement of the flowers which arise in a head from a central point, i.e., bearing an umbel.]

4.7.1 Botany

Litsea umbellata (Lour.) Merr. (*Litsea amara* Bl., *Litsea amara* var. *angusta* Meissn., and *Litsea amara* var. *attenuata* Gamb.) is a lowland forest tree that grows in India and Southeast Asia. The stems are petioles and the midrib is hairy. The leaves are simple, alternate, and exstipulate. The petiole is 5–7mm long. The apex of the blade is pointed or blunt. The base is rounded or cuneate. The midrib above is sunken and there are 9–13 pairs of secondary nerves. The tertiary nerves are scalariform. The blade is glaucous below. Axillary short racemes run off peduncled umbellules. Fruit is elliptic, up to 1cm long, black, glossy, and seated on a 4–6-lobed perianth (Figure 4.8).

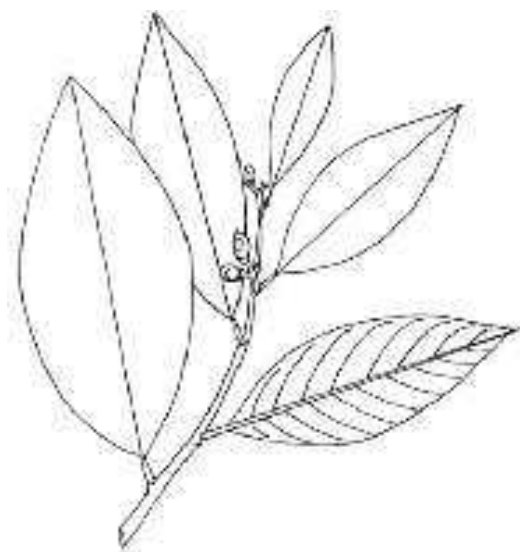


Figure 4.8 *Litsea umbellata* (Lour.) Merr. [From: Flora of Malaya Peninsula Forest Department. Geographical localization: Jalan Kulam ayer Raub, Pahang, Dec. 27, 1929. No: 20473. Field collector: Kalong. Botanical identification: J. G. H. Kosterboils. 1968.]

Figure 4.8 *Litsea umbellata* (Lour.) Merr. [From:

4.7.2 Ethnopharmacology

Flora of Malay Peninsula. Forest Depart

ment. Geographical localization: Jalan

Kulam ayer Raub, Pahang. Dec. 27,

The plant is known as *medang ayer* in Indo

1929. No: 20473. Field collector: Kalong.

Malaya; the leaves are used as a poultice to heal

Botanical identification: J. G. H. Kosterboils. The pharmacological potential of this mans, Jan. 1, 1968.] plant is unknown. Both (+)-demethoxyepiexcelsin and verticillatol from *Litsea verticillata* have anti-HIV properties.⁵ An interesting development would be the evaluation of Lauraceous lignans for antiviral properties.

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CHAPTER 5

Medicinal Plants Classified in the Family Piperaceae

5.1 GENERAL CONCEPT

The family Piperaceae (C. A. Agardh, 1825 nom. conserv., the Pepper Family) consists of 10 genera and about 2000 species of tropical plants of which about 30 species are medicinal in Asia–Pacific. In field collection, Piperaceae can be recognized by three main features: articulate stems, asymmetrical or cordate leaves, and axillary spikes of little round berry-like fruits (Figure 5.1). Black Pepper (*British Pharmacopoeia*, 1949) and Long Pepper (*Indian Pharmaceutical Codex*, 1955), which consist of the dried unripe fruits of *Piper nigrum* L. and *Piper longum*, have been used since time immemorial in India. Black pepper at doses ranging

from 300–600mg stimulates the tastebuds, produces a reflex increase in gastric secretion, reduces fever, and promotes urination. White pepper consists of dried unripe fruits of *Piper nigrum* L. deprived of the outer part of the pericarp. The taste of peppers is due to piperine, a piperidine alkaloid. The dried unripe fruit forms the condiment, cubeb. Cubeb (*British Pharmaceutical Codex*, 1934) consists of the dried unripe fully grown fruit of *Piper cubeba* L. f. It was formerly employed as a urinary antiseptic (liquid extract: 1-in-1 dose 2–4 mL). Lozenges of cubeb have been used to treat bronchitis. Cubeb Oil (*British Pharmaceutical Codex*, 1949) is the oil obtained by distillation of cubeb. It has been used as an emulsion or in capsules as a urinary treatment. Other Piperaceae of relative pharmaceutical value are *Piper methysticum* Forst. (Kava, *British Pharmaceutical Codex*, 1934) and *Piper betle* (*British Pharmacopoeia*, 1934). A beverage prepared from the roots (Buy now from <http://www.drugswell.com>) of *Piper methysticum* Forst. or kava has been used for centuries to calm and to promote sleep by a number of Polynesian

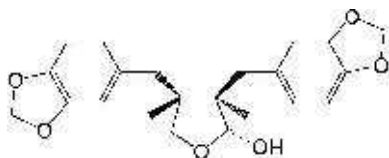


Figure 5.1 Piperaceae leaf showing the characteristic heart-shaped leaf with prominent veins.

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Piperine

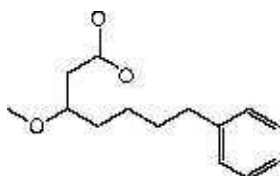


(-) – Cubebin

H OH



Bisabolol



Kawain

Figure 5.2 Examples of bioactive natural products from the family Piperaceae.

people and, although toxic, has been marketed in Europe to treat sleep disorders and anxiety. Note that lignans of Piperaceae are of particular interest as a potential source of cytotoxic and antiviral agents (Figure 5.2).

5.2 *PIPER ABBREVIATUM* OPIZ

[From: Latin *piper* = pepper and *abbreviatum* = shortened or abbreviated in some fashion.]

5.2.1 Botany

Piper abbreviatum Opiz is a branching climber hugging trees with pendent lateral branches. The plant grows in Indonesia and the Philippines. The stems are fissured longitudinally, rooting, 3mm in diameter, and articulated. The leaves are simple, spiral, and exstipulate. The petiole is 8mm long. The blade is elliptic, 8cm – 11cm × 2.2cm – 4cm, acuminate at the apex in a 2.2cm-long tail, and shows two pairs of secondary nerves. The inflorescences are cream-colored spikes, which are axillary, globose, and 1cm in diameter (Figure 5.3).

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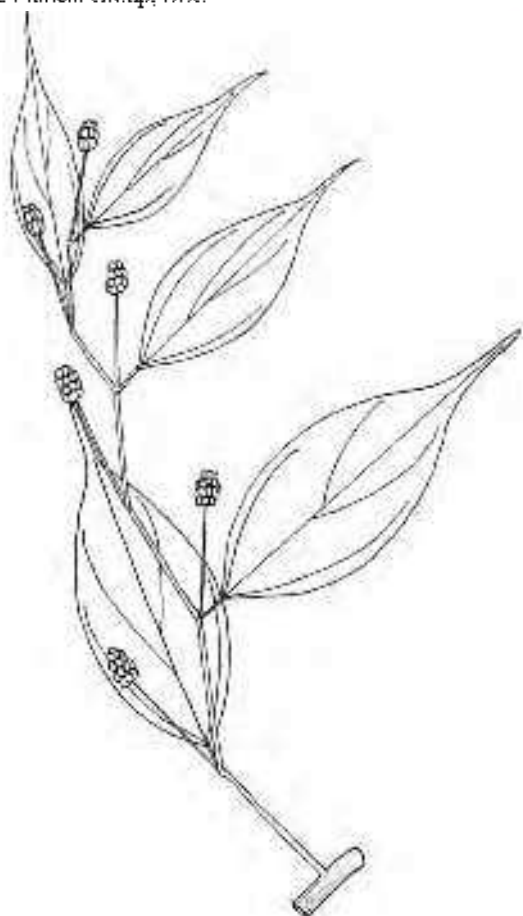


Figure 5.3 *Piper abbreviatum* Opiz. From: *Flora of Borneo*, General University of Science and Technology, Manila, Philippines, 1994. From: *Flora of Borneo*, Geographical Institute of the University of Bonn, Bonn, Germany, 1994. From: *Flora of Borneo*, Geographical Institute of the University of Bonn, Bonn, Germany, 1994.

5.2.2 Ethnopharmacology

In the Philippines, a paste of leaves is used externally to treat splenomegaly. The pharmacological properties of *Piper abbreviatum* Opiz are unexplored. The medicinal property mentioned above might be owed to counterirritant effects. The plant has not been studied for pharmacology.

5.3 *PIPER BETLE* L.

[From: Latin *piper* = pepper and from Malayalam *vettila* = *Piper betle*.]

5.3.1 Botany

Piper betle L. (*Chavica betle*) is a climber that grows in India, Indonesia, Malaysia, the Philippines, Sri Lanka, Vietnam, and China. The stems are dichotomous, articulate, swollen, and rooted at nodes 3mm in diameter, woody, and with 4–2.5cm-long internodes. The leaves are simple, spiral, and exstipulate. The petiole is 5mm long, channeled, and pubescent. The blade is 10cm × 6cm – 9.5cm × 5cm, ovate to ovate-oblong, and light green below. The base of the blade is cordate and the apex is acuminate. The secondary nerves are in three pairs. The inflorescence is an axillary spike, which is 5.5cm long. The fruits are drupaceous, orange, and 3mm in diameter (Figure 5.4).

5.3.2 Ethnopharmacology

Betle (*British Pharmaceutical Codex*, 1934) consists of the dried leaves of *Piper betle*, which has been used as a stimulant, carminative, and antiseptic. It is used in India as a masticatory; in Malaysia, the leaves are usually mixed with lime and the scraping of *Areca* nuts. The plant is known as *lou ye* in China where the leaves

are used as a condiment. The roots (Buy now from <http://www.drugswell.com>), leaves, and fruits are carminative, stimulant, corrective, and used for the treatment of malaria. In the *Pentsao*, an oil obtained from the leaves is used as a counterirritant in swellings, bruises, and sores. In Malaysia, the leaves are applied externally to the body after childbirth. They are also used to heal ulcers, boils, bruises, ulcerations of the nose, and as an antiseptic.

Hydroxychavicol is known to modulate benzo[a]pyrene-induced genotoxicity through the induction of dihydrodiol dehydrogenase, hence the increased potential of betle chewing and smoking in the development of oral squamous cell carcinoma (OSCC).¹ An aqueous extract of the leaves of *Piper betle* given orally during the initiation phase of 7,12-dimethylbenz[a]anthracene (DMBA) induced mammary carcinogenesis in the rodent inhibited the emergence of tumors.² Note that a chloroform extract of *Piper betle* and *Piper chaba* showed some potential against *Giardia* cultured *in vitro*.³

The plant is known to produce phenylpropanoids such as hydroxychavicol and allylpyrocatechol, the latter being antibacterial against oral anaerobes responsible for halitosis.⁴

5.4 PIPER OFFICINARUM DC.

[From: Latin *piper* = pepper and *officinarum* = sold as an herb.]



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5.4.1 Botany

Piper officinarum DC. (*Piper retrofractum* Vahl, *Chavica officinarum* Miq., and *Piper chaba* Hunt.) is a climber that grows in India, Indonesia, China, Malaysia, the Philippines, Thailand, and Vietnam. The stems are 2mm thick, terete, and striated with 4.2–1.8cm-long internodes. The leaves are simple, exstipulate, and spiral. The petiole is 9mm long. The blade is narrowly elliptic, ovate-oblong, or elliptical, 8.5cm – 16cm × 3.2cm – 7.5cm, papery, glaucous, and showing four pairs of secondary nerves and a few tertiary nerves. The inflorescences are 10cm × 4mm spikes attached to 1.5cm-long pedicels (Figure 5.5).

5.4.2 Ethnopharmacology

The plant is known as *kechundai* (Iban) and *jia bi ba* (Chinese). Pepper obtained from this species has been used as an adulterant for *Piper longum*. In Cambodia, Laos, and Vietnam, the plant is used to treat fever, jaundice, rheumatism, neuralgia, and boils. In the Philippines, the roots (Buy now from <http://www.drugswell.com>) are chewed to promote digestion and externally used to heal wounds. The plant elaborates a series of unusual amides such as ridleyamide, brachystamide C, and retrofractamide C, the pharmacological potential of which would be worth assessing; one might set the hypothesis that such compounds mediate the antiinflammatory potential of the plant since retrofractamide B has significantly inhibited indomethacin-induced gastric lesions in the rodent.⁵

5.5 PIPER SARMENTOSUM ROXB.

[From: Latin *piper* = pepper and *sarmentosum* = twiggy, with long, slender runners.]

5.5.1 Botany

Piper sarmentosum Roxb. (*Chavica hainana* DC., *Chavica sarmentosa* [Roxburgh] Miq., *Piper albispicum* DC., *Piper brevicaulis* DC., *Piper gymnostachyum* DC., *Piper lolot* DC., *Piper pierrei*

DC., and *Piper saigonense* DC.) is a shrub that grows to a height of 50cm in Cambodia, India, Burma, Thailand, Indonesia, Laos, Malaysia, the Philippines, Vietnam, and China. The leaves are simple, alternate, and exstipulate. The blade is lanceolate–elliptical, 10cm × 5cm – 14cm × 6cm – 9.9cm × 3.4cm – 12cm × 2cm, acuminate at the apex, rounded at the base, with two pairs of secondary nerves. The inflorescences are 5mm-long nerves. The fruits are green–red with 4mm × 3mm drupes (Figure 5.6).

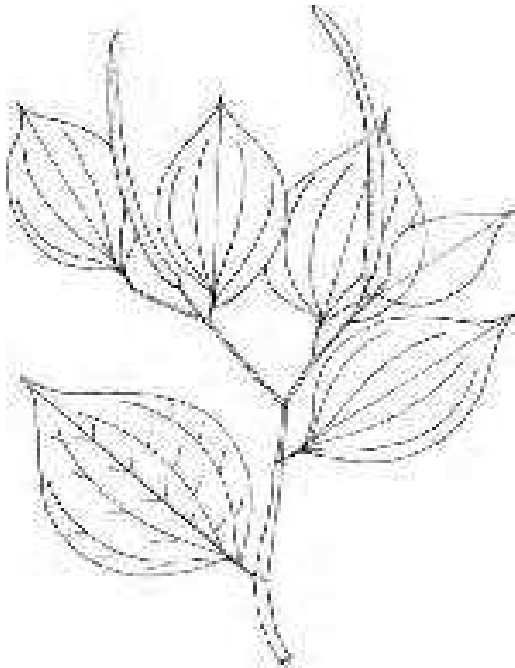


Figure 5.6 *Piper officinale* DC. [From: Field No. 127473, Conservation International, near Anantnag, Jammu & Kashmir, India, 500m, Field No. 127473, 12/1/1987, J. S. Burley and J. S. Burley, in Burley, 1994.]

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Figure 5.6 *Piper sarmentosum* Roxb. [From: Hikmah of Malaya, Hik. No. 19468, Serdang, 1990, the editor.]

M. Asri. Geographical localization: Perak, Ulu Perak, Halong River, ridge trail, Temenggor. In mixed dipterocarp forest.]

5.5.2 Ethnopharmacology

The plant is known as *jia ju* in China where the leaves afford a treatment for fever and indigestion. The roots (Buy now from <http://www.drugswell.com>) are used to assuage toothaches and to treat dermatomycoses. In Malaysia and South Thailand, the leaves are used externally to soothe headaches. In Indonesia, the roots (Buy now from <http://www.drugswell.com>) are chewed for cough, asthma, and toothaches, and the leaves are used externally to mitigate chest pain. In Thailand the plant is called *chaplu*.

An aqueous extract of whole *Piper sarmentosum* Roxb. given orally at a dose of 0.125g/Kg for a week has lowered the glycemia of both streptozocin-induced diabetic rats and normal rats.⁶

Methanolic extract of leaves at concentrations of 3.2, 4.0, 4.8, and 6.4mg/mL exhibited an initially transient increase in twitch tension which was followed by a marked dose-related neurally evoked twitch depression with EC₅₀ of 4.07mg/mL. This effect was antagonized by tetraethylammonium, suggesting neuromuscular blocking activity at the neuromuscular cholinergic junction.⁷ A chloroform extract showed some levels of antiplasmodial activity.⁸ The active principles involved in the antidiabetic properties of *Piper sarmentosum* are unknown. A remarkable advance in *Piper sarmentosum* pharmacological potential has been provided by Rukachaisirikul et al.⁹ They isolated a series of amides including brachystamide B, sarmentine, brachyamide B, 1-piperettyl pyrrolidine, and lignans, and showed that sarmentine and 1-piperettyl pyrrolidine display antituberculosis and antiplasmodial activities. What is the pharmacological potential of amides from Piperaceae in diabetes?

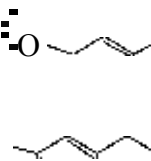
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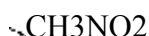
Medicinal Plants Classified in the Family Aristolochiaceae

6.1 GENERAL CONCEPT

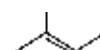
The family Aristolochiaceae (A. L. de H₃CO Jussieu, 1789 nom. conserv., the Birthwort



Family) comprises approximately 5 genera



and 300 species of poisonous climbers, which can be recognized in field collection by their corolla, often shaped like a little



H₃CO

smoking pipe. Several species in this fam



ily have been used for medicinal purposes in the Western world: *Aristolochia reticu-*

Aristolochic acid *Isoboldine*

lata (serpentary, red river snakeroot, and

Figure 6.1 Examples of bioactive natural products

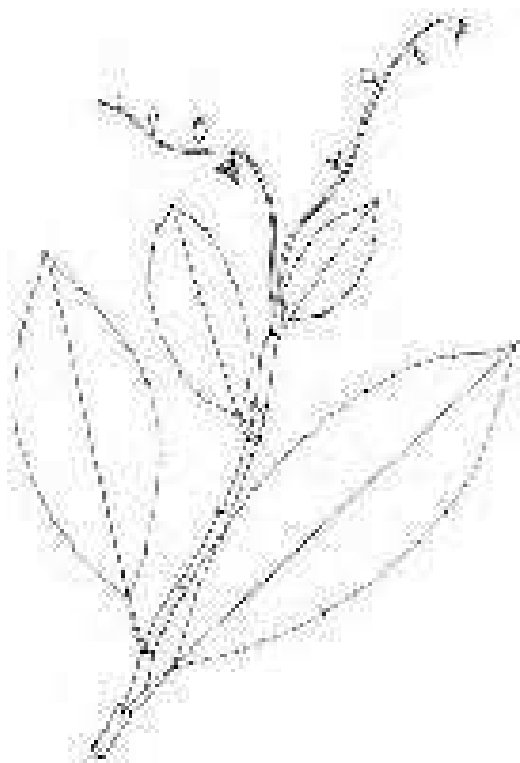
(Texan snakeroot), *Aristolochia serpentaria*

derived from the Aristolochiaceae family.

(Virginian snakeroot), *Aristolochia clematis* (birthwort), and *Asarum europeum* (Asarabaca, *Spanish Pharmacopoeia* 1954). In China, *Aristolochia contorta*, *Aristolochia kaempferi*, and *Aristolochia recurvilabra* have been used in the traditional Chinese system of medicine (Buy now from <http://www.drugswell.com>) since antiquity. Aristolochiaceae have the ability to elaborate a unique series of phenanthrene alkaloids, one of the best examples of which is aristolochic acid (Figure 6.1). The sodium salt of aristolochic acid has been tried as an antiinflammatory agent, but severe nephrotoxicity in humans and carcinogenicity in rodents aborted further developments. The Asia-Pacific region uses about 20 species of Aristolochiaceae for traditional medicine (Buy now from <http://www.drugswell.com>) mainly to counteract snake-poisoning, to promote urination and menstruation, and to assuage stomachaches. It is also used to treat dropsy and skin diseases.

6.2 ARISTOLOCHIA PHILIPPINENSIS WARB.

[From: Greek *aristo* = best and *lochia* = delivery, and from Latin *philippinensis* = from the Philippines.]



6.2.1 Botany

Aristolochia philippinensis Warb. is a climber that grows in the coastal forest of the Philippine Islands. The stems are slightly pubescent, terete, and articulate. The leaves are simple, exstipulate, and spiral. The blade is oblong–lanceolate, serrate, and 5cm – 18cm × 2cm × 5cm. The secondary nerves are inconspicuous. The flowers are arranged in terminal inflorescences. The fruits are capsular, up to 1cm long, and dehiscent (Figure 6.2).

6.2.2 Ethnopharmacology

In the Philippines, a decoction of the roots (Buy now from <http://www.drugswell.com>) is used to assuage stomachache and to promote menses. Note that aristolochic acid and congeners share some similitude in chemical structure with our own steroidal hormones, hence their potency when acting as antiinflammatory and gynecological agents. Aristolochic acid inhibits *in vitro* and dose-dependently phospholipid hydrolysis by the human synovial fluid phos-

Figure 6.2 *Aristolochia philippinensis* Warb. [From: pholipase A2, snake venom phospholipase A2, Plants of the Philippines. Geographical porcine pancreatic phospholipase A2, and localization: Pawalan Island. 9°17'N,

human platelet phospholipase A₂^{1,2} which is a

11°57' E, Alt.: 0–5m. Coastal forest at base of limestone hill, above mangrove key enzyme in inflammation and possibly

formation. D. D. Soejarto and D. A. linked to the release of luteinizing and growth Madulid, July 26, 1982. Botanical identi

hormones from the anterior pituitary.³

fication: June 1994.]

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CHAPTER 7

Medicinal Plants Classified in the Family Nymphaeaceae

7.1 GENERAL CONCEPT

The family Nymphaeaceae consists of 5 genera and 50 species of aquatic rhizomatous herbs which are cosmopolitan in distribution. Nymphaeaceae are known to be an elaborate series of sesquiterpene alkaloids. The leaves arise directly from the rhizome, alternate, long petiolate, hastate, or peltate and floating. The flowers are solitary, axillary, and often showy. The fruits are spongy, often conical, and full of seeds, which are small and scanty. In the Asia-Pacific, *Brasenia schreberi*

J.F. Gmel., *Euryale ferox* Salisb., *Nelumbo nucifera* Gaertn., *Nuphar japonicum* DC., *Nymphaea sellata* Willd., and *Nymphaea pubescens* Willd. are medicinal.

The evidence currently available suggests the family Nymphaeaceae to be an exciting source of cytotoxic, antiviral, and immunomodulating quinolizidine alkaloids; one can reasonably expect the discovery of clinical agents from this family in the relatively near future. Perhaps no other genus in this family has aroused more interest in the field of pharmacology than the genus *Nuphar*. Matsuda et al.¹ made the interesting observation that the rhizome of *Nuphar pumilum* contains dimeric sesquiterpene thioalkaloids, such as 6-hydroxythiobinupharidine, 6,6'-dihydroxythiobinupharidine, and 6-hydroxythionupharlutine B, which inhibited the invasion of B16 melanoma cells across collagen-coated filters *in vitro* with IC₅₀ 0.029, 0.087, and 0.36μM, respectively, indicating **a clear antimetastatic potential** (Figure 7.1). Using antisheep erythrocyte plaque-forming cell for mation in mouse splenocytes assay, Matsuda et al. showed potent immunosuppressive activity of 6-hydroxythiobinupharidine, 6,6'-dihydroxythiobinupharidine, 6-hydroxythionupharlutine B, and 6-hydroxythionupharlutine B, and observed that the 6- or 6-hydroxyl group at the quinolizidine ring of dimeric sesquiterpene thioalkaloids is essential for the immunosuppressive effect.

7.2 NELUMBO NUCIFERA GAERTN.

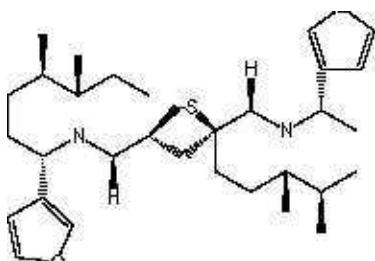
[From: Sri Lankan *nelumbu* = *Nelumbo nucifera* and Latin *nucifera* = nut-bearing.]

7.2.1 Botany

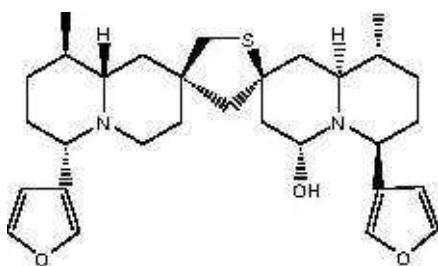
Nelumbo nucifera Gaertn. (*Nelumbium nelumbo* [L.] Druce, *Nelumbium speciosum* Willd., *Nelumbo komarovii* Gross., *Nelumbo nucifera* var. *macrorrhizomata* Nak., and *Nymphaea nelumbo* Linn.) is an aquatic herb that grows in ponds, pools, rivers, and lakes in China, Bhutan, India,

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O



Thiobinupharidine



6-Hydroxythionuphlutine B

Figure 7.1 Examples of bioactive natural products derived from the family Nymphaeaceae.

Indonesia, Japan, Korea, Malaysia, Burma, Nepal, New Guinea, Pakistan, India, the Philippines, Sri Lanka, Thailand, Vietnam, Australia, and the Pacific Islands. The plant grows from a rhizome constricted at its nodes and is somewhat pinkish. The petiole is to 2m long, terete, fistulous, and glabrous. The blade is 25–90cm in diameter, round, thin, glabrous, and entire at the margin. The flowers are conspicuous, 10–25cm in diameter, pink or white, the petals oblong–elliptic to obovate, 5cm–11cm × 2.5cm–5cm. The fruits are conical, green, and up to 15cm long (Figure 7.2).

7.2.2 Ethnopharmacology

In Asia, the fruits of the lotus, or *lian*, *fu chu* (Chinese), and *teratai* (Malay), are sold in the market for the seeds, which are edible and medicinal. In China, the seeds are used to preserve the body's health and strength, to cool, to promote blood circulation, and to treat leucorrhea and gonorrhea. The rhizomes are edible and after cooking they form a sweet mucilaginous food that is taken to assuage a stomachache, to strengthen the body, to increase the mental faculties, and to quiet the spirit. The inflorescence is antihemorrhagic, and given as a postpartum remedy. The leaves are used to break fever, as an antihemorrhagic, to precipitate childbirth, and to treat skin diseases. The petiole is used to quiet the uterus. The flowers are spoken of in the *Pentsao* and believed to drive away old age and to give a fine complexion.

The plant is interesting since it elaborates antiviral isoquinolines (Figure 7.3): (+)-1(R)-coclaurine and 1(S)-norcoclaurine from the leaves of *Nelumbo nucifera* Gaertn., which inhibits the replication of HIV *in vitro* with EC₅₀ values of 0.8 and <0.8g/μL, and therapeutic index values of >125 and >25, respectively. Liensinine and isoliensinine showed potent anti-Human Immunodeficiency Virus (HIV) activities with EC₅₀ values of <0.8g/μL and Therapeutic Index values of >9.9 and >6.5g/μL. Nuciferine, an aporphine alkaloid, had an EC₅₀ value of 0.8g/μL and a Therapeutic Index value of

36.² Isoliensinine exhibited a significant inhibitory effect on bleomycin-induced pulmonary fibrosis

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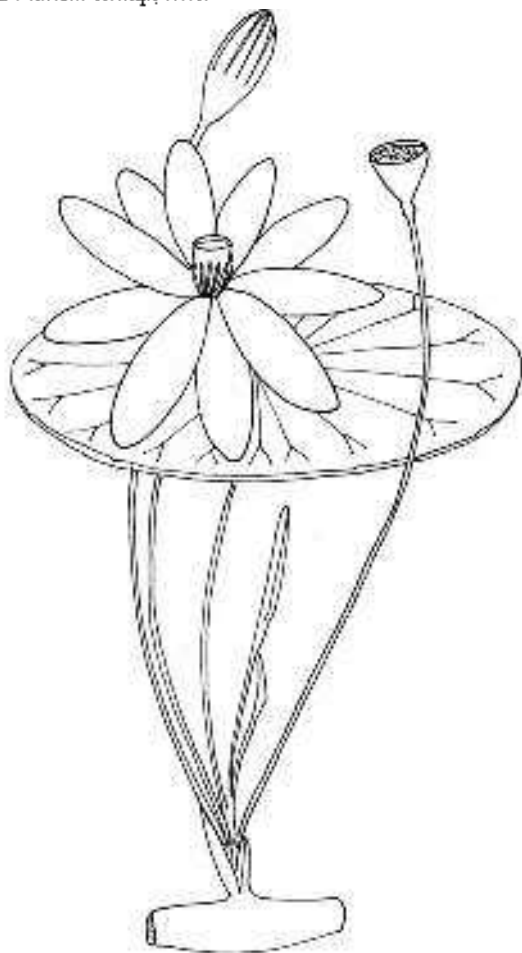


Figure 1.2 *Nelumbo nucifera* Gaertn. (Hornem.) Bl. & No. 25712. Geographical localization: Vietnam (red-tille). Oct. 19, 1976. Field collection and technical illustration: M. A. J.

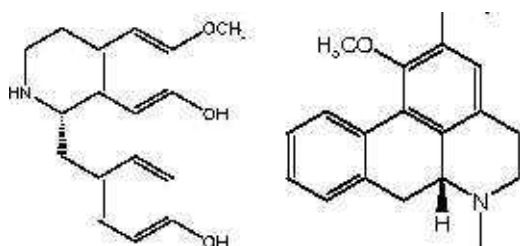
in male mice. The alkaloid lowered the hydroxyproline content and limited the lung histological injury induced by bleomycin, and also inhibited the overexpression of TNF-alpha and TGF-beta induced by bleomycin, and showed potent activity against bleomycin-induced pulmonary fibrosis.³

The antiinflammatory property of *Nelumbo nucifera* Gaertn. is confirmed *in vitro* and *in vivo*. A methanol extract of rhizomes given at doses of 200mg/kg and 400mg/Kg showed significant antiinflammatory activity in models of inflammation in rats as efficiently as phenylbutazone and dexamethasone.⁴

An extract inhibited proliferation in human peripheral blood mononuclear cells activated with phytohemagglutinin on account of NN-B-4 which is mediated, at least in part, through inhibition of early transcripts of interleukin (IL)-2, interferon (IFN)- γ , and cdk4, and arrest of cell cycle progression in the cells.⁵ An ethanol extract of the petiole lowered normal body temperature in a dose of 200mg/Kg, while in yeast-induced fever it showed a dose-dependent lowering of body temperature as efficiently as paracetamol.⁶

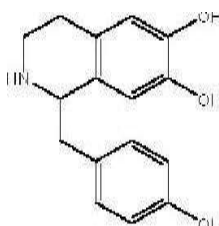
Ethanol extract from seeds of *Nelumbo nucifera* showed antioxidant and hepatoprotective effects.⁷ Oral administration of the ethanolic extract of rhizomes lowered the blood glucose levels of normal, glucose-fed hyperglycemic and streptozotocin-induced diabetic rats, and improved glucose tolerance, and also potentiated the action of exogenously injected insulin in normal rats.⁸

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Coclaurine Nuciferine

Norcoclaurine



Liensinine

Figure 7.3 Antiviral alkaloids of *Nelumbo nucifera* Gaertn.

When compared with tolbutamide, the extract exhibited activity of 73% and 67% of tolbutamide in normal and diabetic rats, respectively.

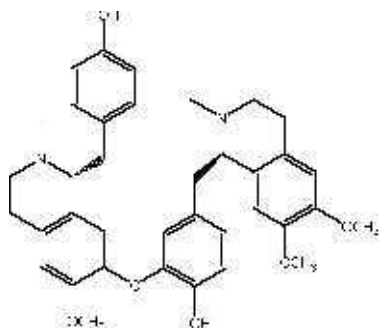
Methanolic extract of rhizomes lowered spontaneous activity, decreased the exploratory behavioral pattern, and potentiated pentobarbitone-induced sleeping time in rats.⁹

7.3 NYPHEA PUBESCENS WILLD.

[From: Greek *nymphaia*, referring to a water nymph, and from Latin *pubescens* = with soft, downy hair.]

7.3.1 Botany

Nymphaea pubescens Willd. (*Nymphaea lotus* L. var. *pubescens* (Willdenow) J.D. Hook. & Thoms.) is an aquatic herb which grows from a 10cm rhizome. It is found in lakes, pools, and rivers in a geographical area spanning Queensland, Papua New Guinea, India, and Southeast Asia. The petiole is up to 2m long. The blade is elliptic to orbicular, up to 45cm in diameter, hairy below; dentate at the margin. The flowers are showy and white above water. The calyx comprises 4–5cm, up to 9cm-long, obtuse sepals. The corolla has 19 petals that are oblanceolate and pinkish. The androecium consists of 60 flattened, thickened stamens with 2cm anthers. The gynoecium consists of 11 to 20 carpels united to form a plurilocular ovary (Figure 7.4).



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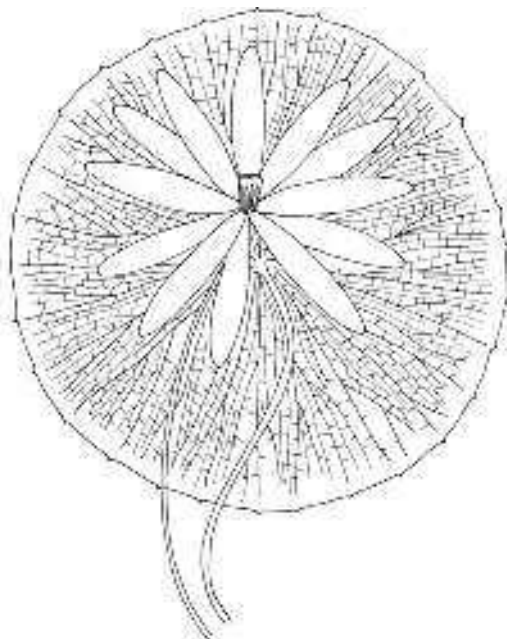


Figure 7.4 *Nymphaea pubescens* Willd. [From: *Fl. Ind. Néerl.*, vol. 4, p. 295, 1805.]

7.3.2 Ethnopharmacology

Water lilies or *rou mao chi ye shui lian* (Chinese) are used in the Philippines to treat gonorrhea. It is also rubbed on the forehead to induce sleeping. The pharmacological property of this plant is unexplored. Are alkaloids with hypnotic properties present in this plant?

7.4 NYPHEA STELLATA WILLD.

[From: Greek *nymphaia*, referring to a water nymph, and from Latin *stellata* = star-like shaped.]

7.4.1 Botany

Nymphaea stellata Willd. (*Nymphaea nouchali* Burm. f., *Nymphaea minima* F.M. Bailey) is an aquatic herb that grows from a tuberous rhizome to 5cm in diameter in Australia, Papua New Guinea, Southeast Asia, and India in swamps and pools. The blade is 12.5cm × 35cm and the petiole is 20cm. The flowers are white. The calyx consists of four sepals which are 3cm long, green outside with purplish penciling. The corolla comprises 10 petals which are lanceolate, blue, pink, or white. The androecium consists of 20 stamens which are yellow. The flower pedicel is 13.5cm × 2mm. The flower bud is 4.2cm × 2.2cm (Figure 7.5).

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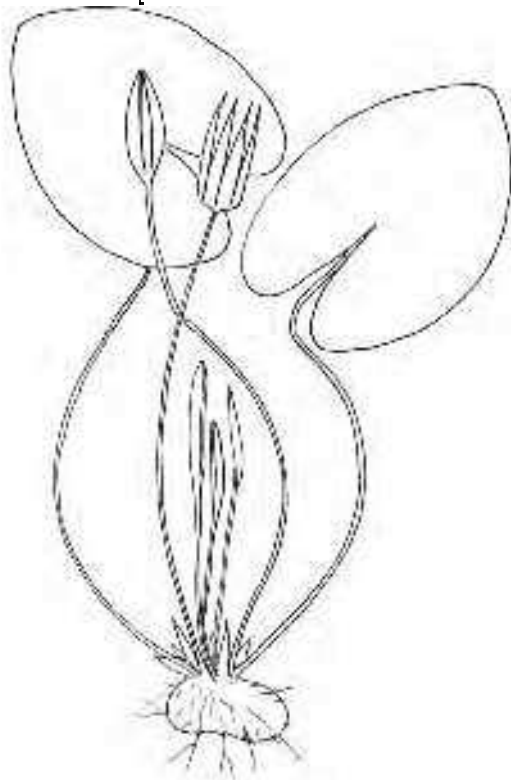


Figure 7.5 *Nymphaea stewartii* Willd. From: HSI No. 2765. Road between Ulaa K'aw and Kuala Lumpur, Pahang, Malaysia (collected by the author, August 2004; F.S. F. 46, 46, 10/1971)

7.4.2 Ethnopharmacology

The plant is known as *talipok* in Borneo and *yan yao shui lian* in China. In Laos, Cambodia, and Vietnam, the leaves are used externally to break fever, while the rhizomes are used to treat gastrointestinal disturbances. In India, the plant is used to treat liver disorders. An extract of flowers has protected albino rats against carbon tetrachloride-induced hepatic damage when given orally for 10 days.¹⁰ What are the principles involved here? Thioalkaloids!

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CHAPTER 8

Medicinal Plants Classified in the Family Menispermaceae

8.1 GENERAL CONCEPT

There are approximately 40 species of plants classified within the family Menispermaceae (A.

L. de Jussieu, 1789 nom. conserv., the Moonseed Family). They are used for medicinal purposes in the Asia-Pacific, particularly to mitigate fever, as a diuretic, emmenagogue, carminative, tonic, antiinflammatory, and analgesic. The family Menispermaceae consists of 70 genera and approximately 400 species of tropical climbers that have attracted a great deal of interest on account of their ability to elaborate a series of diterpenes, benzyloquinoline, and aporphine alkaloids. When looking for Menispermaceae for field collection, it is suggested to look for climbers in which the transverse section of the stem shows a very characteristic bicycle wheel-like aspect and a bright, yellowish color. Other distinctive features are the slender petiole often twisted at the base, leaves with a few nerves, and particularly the seeds which are muricate and horseshoe-like.

With regard to the pharmaceutical potential of Menispermaceae, *Anamirta paniculata* Coleb. (Levant berries) has been used in Western medicine (Buy now from <http://www.drugswell.com>) to promote appetite and digestion on account of its bitterness. The dried transverse slices of roots (Buy now from <http://www.drugswell.com>) of *Jateorrhiza palmata* Miers (Calumba, *British Pharmaceutical Codex*, 1954) are said to be a remedy for atonic dyspepsia; the dried stems of *Tinospora cordifolia* (Tinospora, *Indian Pharmaceutical Codex* 1953) have been used to promote digestion and appetite in the form of an infusion.

Examples of isolates of pharmaceutical interest are picrotoxin and tubocurarine (Figure 8.1). Picrotoxin is found in the seeds of *Anamirta cocculus* (*Anamirta paniculata*) and has been used for the treatment of barbiturate poisoning in the form of injection 3–6mg, intravenously (Picrotoxin, *British Pharmacopoeia*, 1963). Picrotoxin consists of a mixture of picrotoxinin and picrotin, picrotoxinin being a sesquiterpene with specific GABA_A receptor-blocking activity, which impedes the GABAergic presynaptic inhibition of excitatory transmission of primary afferent neurones of the spinal cord. Picrotoxin is toxic, and as little as 20mg induces epileptiform convulsions, myosis, and dyspnea with more or less prolonged apnea.

Several Amazonian tribes have been using Menispermaceae from the genera *Chondrodendron*, *Curarea*, *Sciadotenia*, *Abuta*, *Telotoxicum*, and *Cissamplelos* to make arrow poisons or curares which abound with bis-benzyltertrahydroquinoline alkaloids such as (+)-tubocurarine, (+)-isochondrodendrine, (–)-curine, and (+)-chondrocurine. These alkaloids are anticholinergic at the neuromuscular synapse and provoke drastic relaxation of the skeletal muscles; hence their uses in surgical anesthesia (Tubocurarine Chloride, *British Pharmacopoeia*, 1963).