
2 Plants Affecting the Central Nervous System

GENERAL CONCEPT

The use of plants to influence brain function has long been essential to medical practice, and one could say that the intake of new plant species by early hominids resulting from a change in the climate might have triggered the Mind's Big Bang 50,000 years ago which allowed us to prevail over the Neanderthals, who co-existed with us for tens of thousands of years.

With the arrival of *Homo sapiens* about 35,000 years ago, the first healers or shamans ingested or smoked mushrooms and plants in order to get into a trance and would mentally “fly” to another level of reality, in which they could communicate with animal spirits tell the hunters where preys were likely to be found.

Our early ancestors cultivated Valeriana (*Valeriana officinalis* L., Valerianaceae), hemp (*Cannabis sativa* L., Cannabinaceae), and opium (*Papaver somniferum* L.), the vestiges of which have been found in Croc-Magnon caves. Hippocrates mentions in the *Corpus Hippocraticum* three Solanaceae: *Hyoscyamus niger* (henbane), *Atropa belladonna* L. (belladonna), and *Mandragora officinarum* L. (mandrake), which were used later by witches to enter into delirium. The root of *Mandragora officinarum* L., with its human shape, played a prominent role in the European pharmacopeia of the Middle Ages, and had the reputation of being an aphrodisiac.

From earliest times, curious beliefs about the Human-shaped roots grew up. The Greeks considered the roots as human dwarfs. Theophrastus mentioned that at his time, the collection of Mandrake was following curious rituals including dances and recitation of formulas. During the Middle Ages it was believed that when being pulled from the ground, the plant would let out such a horrible scream that whoever heard the noise might die at once or become insane. Eventually, only black dogs were employed to extract the root, after which, according to belief, the animal usually died. In Central America, *Lophophora williamsii* (*Echinocactus williamsii* [Lem. ex Salm-Dick] Coult.), or peyote, peyotl, anhalonium, or mescal button, has been used to cause hallucination. Peyote contains mescaline, the clinical properties of which are similar to those of lysergic acid diethylamide (LSD).

Classical examples of Asian medicinal plants are *Papaver somniferum* (opium, Papaveraceae), *Cannabis sativa* L. (cannabis, Cannabinaceae), and *Myristica fragrans*

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(nutmeg, Myristicaceae). *Papaver somniferum* was native to the Middle East and is possibly the oldest known narcotic; as early as 4000 BCE the Sumerians referred to it as the "joy plant." Opium was known by the Greeks for its constipating effect and sleep-inducing properties, and Celse mention it his *De re Medica* in about 30 BCE. The plant was brought to India and China by the Arabs, and Barbosa mentions the cultivation of opium in India in 1511. The medicinal use of opium was well established, and control of the opium trade was a central issue during the wars in China in 1839. Opium (*British Pharmacopoeia*, 1963), or the dried latex obtained by incision from the ripe capsules containing not less than 9.5% of anhydrous morphine, has been used as an analgesic and narcotic, and morphine, the active constituent, is used for the abrogation of pain.

Cannabis sativa L. (cannabis, *British Pharmaceutical Codex*, 1949) consists of the dried flowering or fruiting tops of the male *Cannabis sativa* L. It was used by the Chinese and Indians 3500 years ago to induce narcosis. According to Herodotus, hemp was brought by the Scythians in the Mediterranean when they invaded in about 1500 BCE, before the battle of Troy. Herodotus mentions in 600 BCE that the Scythians burned its seeds to produce a narcotic smoke. Dioskurides mentions that if the seeds of cannabis are eaten too freely, they destroy the virile powers, and that the juice is used to relieve earache. Galen asserts that in his time (Middle Ages), it was customary to give hemp seeds to the guests at banquets in order to promote hilarity and enjoyment (1). The British physicians of the army of India (2) and Bonaparte's expedition to Egypt were responsible for its introduction into Europe in the 19th century. There it was consumed in intellectual circles, and the illicit use of cannabis spreaded rapidly. By 1972, at least 2 million Americans used marijuana daily. Cannabis (*British Pharmaceutical Codex*, 1949) has been used in Western medicine to treat mania and nervous disorders, as a cerebral sedative, and as an analgesic for migraine, headaches, and even herpes zoster. The active principle is a phenolic substance known as Δ -9-tetrahydrocannabinol (THC), which binds to the anandamide receptor, which might have potential in the treatment of various symptoms associated with disorders ranging from multiple sclerosis to AIDS to terminal cancer.

The dried kernels of the seeds of *Myristica fragrans* (nutmeg, *British Pharmaceutical Codex*, 1963) are aromatic and carminative. It was not known by the ancient Greeks and Romans, but was used by Indians and Arabs as early as 700 BCE. It was later introduced into Europe by Arab traders and, subsequently, by Portuguese and Dutch merchants. Reports on nutmeg intoxication date back to the Middle Ages, when William Cullen wrote about a patient in his treatise on the *Materia medica* in 1789: "About one hour after he had taken it (nutmeg), he was sized with a drowsiness, which gradually increased to a complete stupor and insensibility, waking from time to time he was quite delirious; and he thus continued alternately sleeping and delirious for several hours." The active principle in nutmeg is myristicin, a catecholamine-like phenylpropanoid.

The most fascinating aspect of the mechanism by which medicinal plants affect the brain function is their ability to elaborate molecules that are able to cross the hematoencephalic barrier and infiltrate the brain where binding to protein receptors occurs.

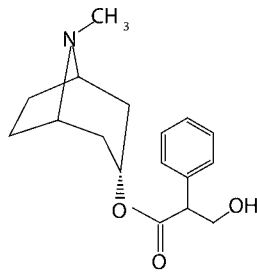
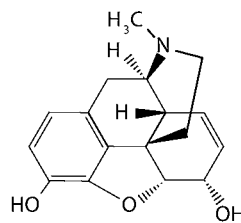
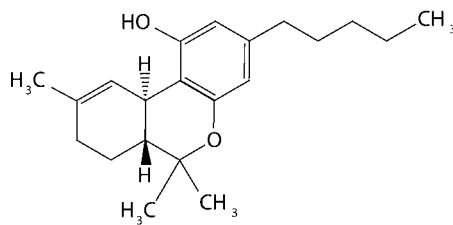
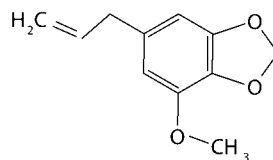
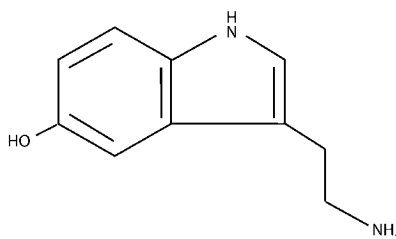
**Atropine****Morphine****Tetrahydrocannabinol****Myristicin**

Fig. 30. Examples of natural products affecting the central nervous system.

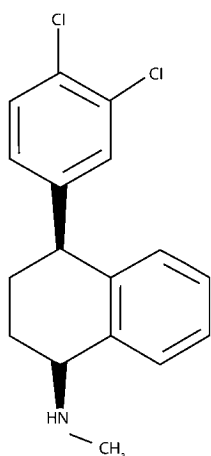
One might set the hypothesis that the medicinal flora of Asia and the Pacific might hold a number of original molecules with potential for the treatment of central nervous disorders. The purpose of this chapter is to bring light onto some families and species of plants with such potentials, and to provide a basis for understanding the many mechanisms by which these herbs influence brain function, including their effects on the serotonergic, γ -aminobutyric acid (GABA)ergic, glycinergic, and dopaminergic systems and opiate receptors.

PLANTS AFFECTING SEROTONINERGIC NEUROTRANSMISSION

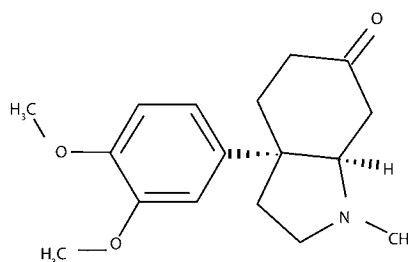
5-Hydroxytryptamine, or serotonin, is a neurotransmitter in the central nervous system (CNS). The nerve-cell bodies of the major serotonergic neurones are in the midline raphe nuclei of the rostral pons, and ascending fibers innervate the basal ganglia, hypothalamus, thalamus, hippocampus, limbic forebrain, and areas of the cerebral cortex. The serotonergic system plays an important role in the control of mood and behavior, motor activity, hunger, thermoregulation, sleep, certain hallucinatory states, and some neuro-endocrine mechanisms.



Serotonin



Sertraline (Zoloft®)

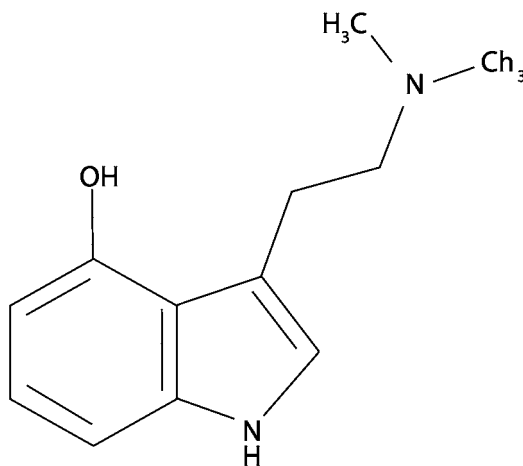


Mesembrine

5-Hydroxytryptaminergic ($5HT_{1A}$) receptors mediate in the CNS the autonomic control of hypothermia, hyperphagia, analgesia, blood pressure, venereal disease, anxiety, and several behavioral paradigms. It has been hypothesized that the anxiolytic property of buspirone is the result of a blockade of $5HT_{1A}$ receptors. Methysergide, a partial $5HT_1$ agonist, and sumatriptan, a $5HT_{1D}$ agonist, are drugs used to assuage headache.

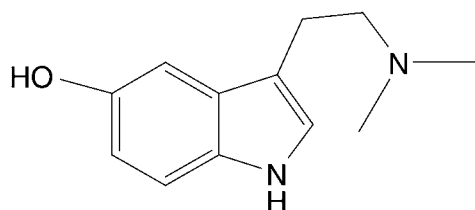
Plants affecting the serotonergic neurotransmission are therefore interesting because of their potentials for the treatment of depression, which is the eighth leading cause of death in the United States. It is generally agreed that there is a correlation between diminished serotonin neurotransmission and episodes of major depression, and a number of inhibitors of serotonin-uptake inhibitors are available on the market, such as sertraline (Zoloft®).

This type of action is found in kanna, or *Sceletium expansum* and *Sceletium tortuosum* (Aizoaceae), which have been used by South African shamans from prehistoric times to “enhance animal spirits, sparkle the eyes, and to stimulate gaiety.” The active constituent of kanna is a serotonin-like alkaloid called mesembrine, which is a potent serotonin re-uptake inhibitor—hence, some potential for the treatment of anxiety and depression; however, careful clinical trials must be performed.



When looking for plants affecting serotonergic neurotransmission, one might look into species that produce indole alkaloids, such alkaloids being known to impart to the plant's hallucinogenic properties.

Such alkaloids can be found particularly in the Myristicaceae, Malpighiaceae, Rutaceae, Apocynaceae, Rubiaceae, Loganiaceae, and Convolvulaceae. Such compounds are also found in mushrooms from the genera *Conocybe*, *Panaeolus*, *Psilocybe*, and *Stropharia* (Agaricaceae), which were used by the Aztecs of pre-Columbian America for their psilocin.



Bufotenine

Another example is bufotenine from Mimosaceae, *Anadenanthera peregrina* (L.) Spreg. (*Piptadenia peregrina* Benth.), a plant known as *yopo*, and a constituent of hallucinogenic snuffs in the Orinoco basin. *Banisteria caapi*, *Banisteria inebrians*, *Banisteria quitensis*, *Banisteria rusbyana*, and *Tetrapteris methystica* from the family Malpighiaceae are used to make a narcotic drink known as *caapi* in Brazil, *yage* in Columbia, and *ayahuasca* in Ecuador, Peru, and Bolivia that is an important tool of Amazonian religious ceremonies. The hallucinogenic and telepathic principles are a series of β -carboline derivatives, including harmine (banisterine, telepathine) and harmaline, the chemical structure of which is very much like serotonin and acts as a 5HT receptor agonist (Fig. 31). These alkaloids cause nausea, dizziness, and general malaise, together with paraesthesia of the hands, feet, and face, followed by numbness, dreams involving the stimulation of midbrain reticular formation, leading to such phenomena as double contours and persistence of after-images. Because of the growing interest in looking for serotonergic agents, we shall consider the pharmacological potentials of the medicinal flora of Asia and the Pacific, and examine the molecules through which they are thought to act.

Medicinal Annonaceae



The family Annonaceae consists of about 120 genera and more than 2000 species of tropical trees, shrubs, or climbers, about 60 species of which are used for traditional medicine in Asia and the Pacific. Annonaceae have attracted a great deal of interest on account of their ability to elaborate isoquinoline alkaloids, which bind to the receptors of serotonin. Anonaine, nornuciferine, and asimilobine from *Annona muricata* L. block 5HT_{1A} receptors (3). Such a property is not surprising because the molecular structures of anonaine, nornuciferine, and asimilobine are similar to the chemical structure of serotonin. For instance, anonaine, nornuciferine, and asimilobine from *A. muricata* L. block 5HT_{1A} receptors, thereby substantiating the anxiolytic use of the plant. Among the medicinal Annonaceae used in Asia, two possible candidates for the characterization of serotonergic alkaloids are *Fissistigma lanuginosum* (Hook.f. & Thoms.) Merr. and *Cyathostemma micranthum* (A. DC.) J. Sinclair.

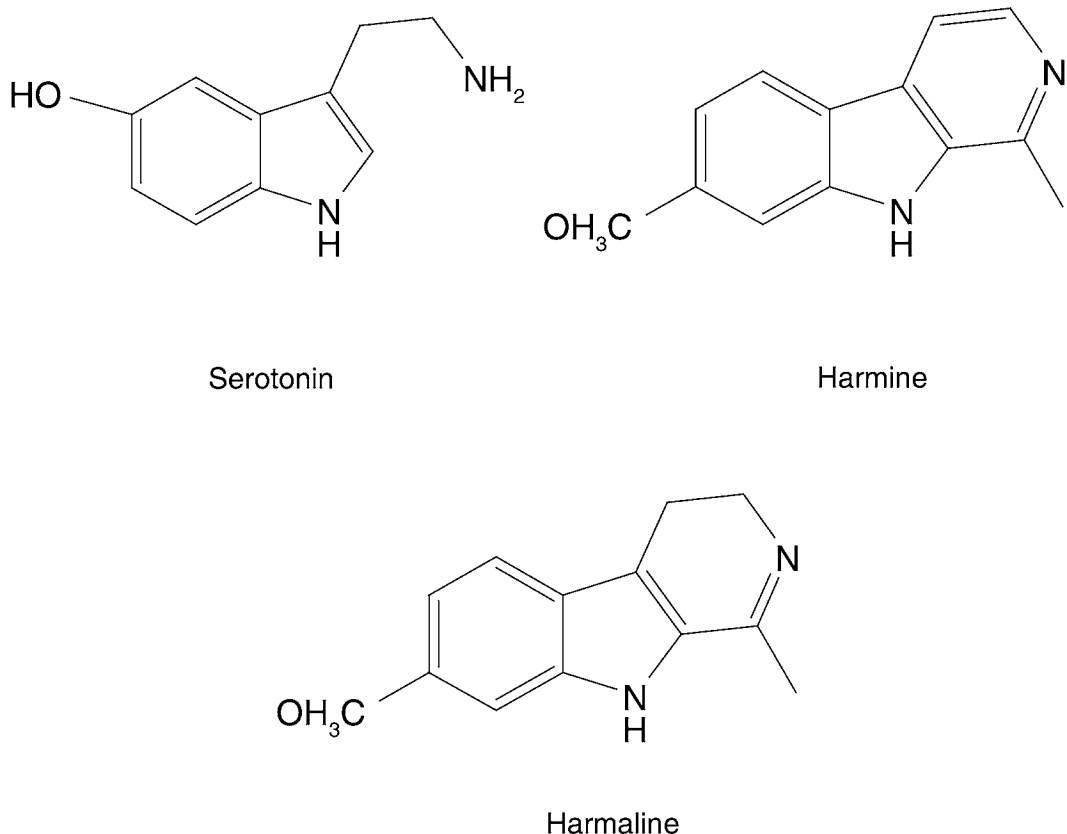
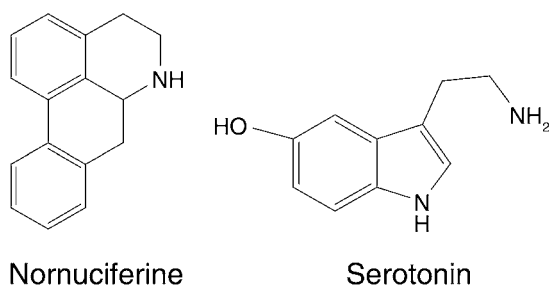


Fig. 31. Example of neuroactive indole alkaloids from plants. Note the similitude of chemical structure of harmine, harmaline, and serotonin.



Fissistigma lanuginosum (Hook.f. & Thoms.) Merr. (*Uvaria tomentosa* Wall., *Melodorum lanuginosum* Hk f. et Th.) is a climber of the rainforests of Malaysia, Vietnam, Cambodia, Laos, and Thailand. The young stems are rusty tomentose. The leaves are simple, exstipulate, alternate, glossy, dark green, thick, and oblong. The fruits are velvety and globose to and grow up to 2 cm in diameter (Fig. 32).

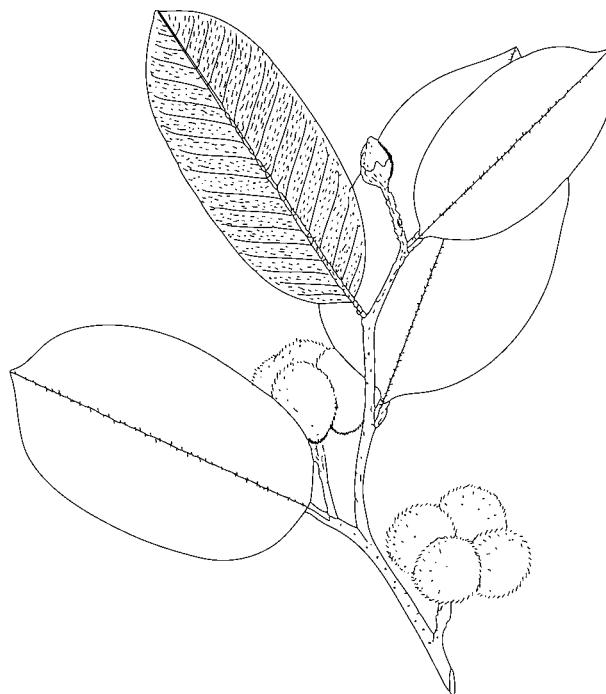
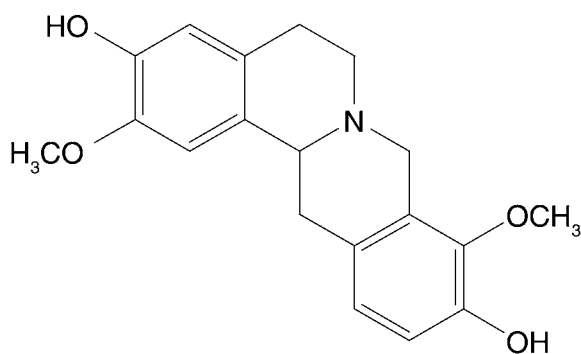


Fig. 32. *Fissistigma lanuginosum* (Hook. f. & Thoms.) Merr. From FRI Herbarium 023427. Flora of Malaya. Geographical localization: National Park, altitude: 700 feet in primary forest.

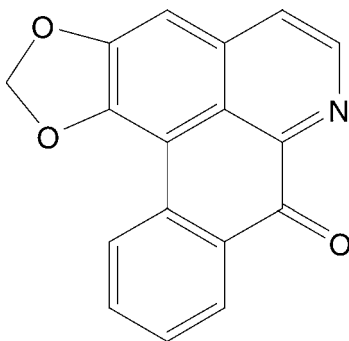


Discretamine

In Malaysia, a decoction of the roots is drunk to assuage stomachaches. The potential of this climber as a source of molecules affecting the serotonergic neurotransmission would be worth investigating because (-)-discretamine characterized from *Fissistigma glaucescens* blocks α_1 - and α_2 -adrenoceptor and exerts a 5-hydroxytryptamine-

antagonist activity. Note discretamine is spasmolytic, hence the use of the plant receptors (4).

Cyathostemma micranthum (A. DC.) J. Sinclair. (*Guatteria micrantha* A. DC, *Uvaria micrantha* Hk. f. et Th.), *Uvaria sumatrana* Kurz, *Anaxagorea sumatrana* Miq, *Cyathostemma sumatrana* Boerl, *Polyalthia fruticans* A. DC, *Popowia nitida* King), or *subang hitam* (Malay), is a climber that grows in the primary rainforest of Thailand, Burma, Malaysia, and east to Papua New Guinea. The roots have a very pleasant ginger-like fragrance. The stems are fissured and dark colored. The leaves are simple, oblong-lanceolate. The fruits are 1-cm-in-diameter ripe carpels with irregular bulges owing to the seeds (Fig. 33).



Liriodenine

In Malaysia, a decoction of the leaves or roots is drunk as a protective remedy after childbirth, and the plant is used to stimulate sexual desire and to invigorate. It is also used to promote sweating and to treat cough. The plant has not been yet investigated for pharmacology but one could suggest that the aphrodisiac and tonic properties might result from a mood elevation via inhibition of serotonin re-uptake. Note that the root of *Cyathostemma argenteum* contains liriodenine and discretamine (5). Liriodenine is known to block muscarinic receptors, but knowledge on its effects on the serotonergic system is quite vestigial (6).

Medicinal Myristicaceae

The family Myristicaceae has about 16 genera and 380 species of tropical lowland rainforest trees that are easily recognizable in field collection because of their blood-like sap, conical crown, and nutmeg-like fruits. A very interesting feature of Myristicaceae species are their ability to elaborate series of neuroactive indole alkaloids, because it produces neuroactive indole alkaloids, which might hold potential for the treatment of anxiety, mood disorders, and other psychological disturbances.

Such alkaloids are *N*, *N*-dimethyl tryptamine, 5-methoxy-*N*, *N*-dimethyl tryptamine, and 2-methyl-1, 2, 3, 4-tetrahydro- β -carboline, which have been characterized from the resins of several *Virola* species, which is used by the witch doctors of several

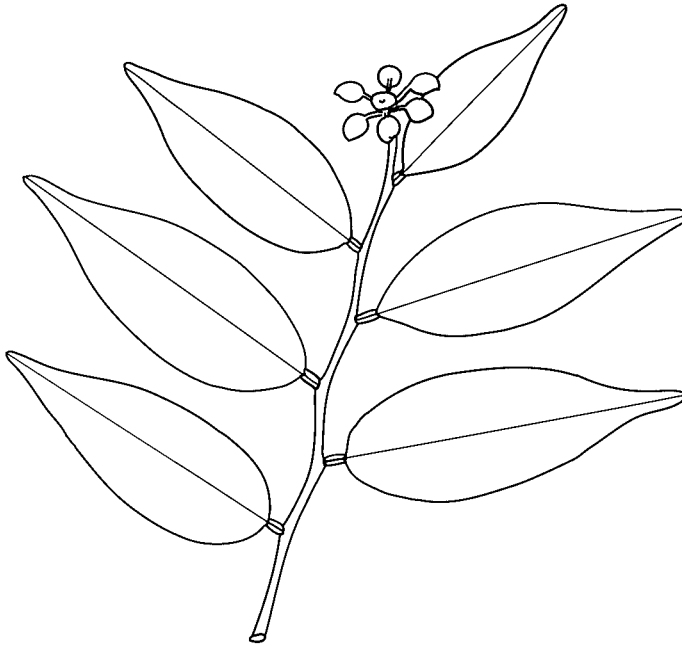
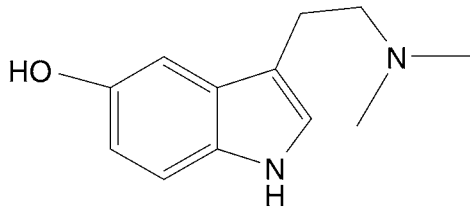
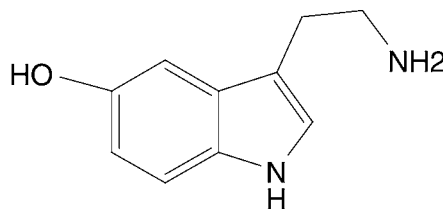


Fig. 33. *Cyathostemma micranthum* (A. DC.) J. Sinclair. From Herb. Hort. Bot. Singap. Field Collector: Burkill & Haniff, 11/24/1924. Geographical localization: Jerantut, Malaysia. Botanical Identification: J. Sinclair, 12/17/1948.

tribes in the Colombian Amazon to make a particularly intoxicating snuff known as *yakee*.



5-Hydroxy-*N*, *N*-dimethyl tryptamine



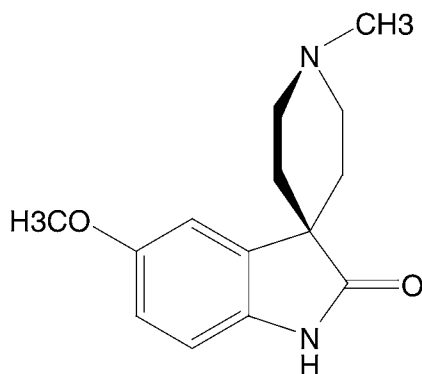
Serotonin



Fig. 34. *Horsfieldia glabra* (Bl.) Warb. Plants of Indonesia. East Bali, Karangasem, South slope of Gunung Agung, 1–2 km Southwest of Basket. Altitude: 750 m. 8° 21' South–115° 26' East in disturbed forest in ravine canopy.

According to Schultes, snuffing *yakee* produces scarily true hallucinations and an exhilarating euphoria. The subject performs prodigious feats of magic and strength because of a superhuman quality (7). About 20 species of plants classified in the family Myristicaceae are medicinal, including *Myristica fragrans* Houtt. (mentioned earlier), as well as a few *Horsfieldia* species, including *Horsfieldia glabra* (Bl.) Warb.

***Horsfieldia glabra* (Bl.) Warb.**, or *feng chui nan* (Chinese), *kayu anak* (Indonesia), is a tree of up to 25 m tall that grows in Thailand, Malaysia, Indonesia, and China. The leaves are oblong-lanceolate, $13.8 \times 3.8 - 15 \times 4.9$ cm, and show 7 to 10 pairs of secondary nerves. The fruits are ovoid to elliptical, 1.5–2.5 cm, orange color, aril orange color, and completely enclose seeds. In Indonesia, the bark and leaves are used to treat intestinal disturbances. The bark is also used to heal sores and boils on probable account of arylalkanonones (8).



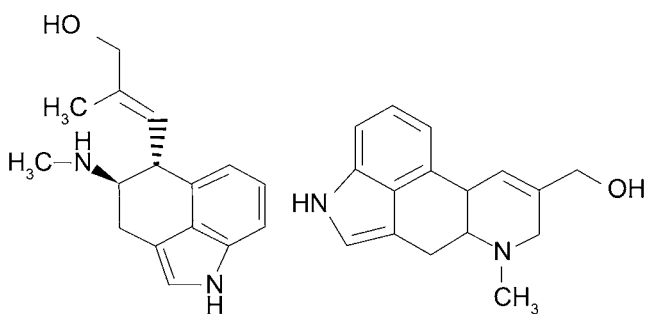
Horsfiline

One might set the hypothesis that intestinal disturbances, which are a common symptom in depression, could be the result of a serotonin-like mechanism because the *Horsfieldia* species, including *Horsfieldia superba* (Hk. f. et. Th.) Warb., are known to elaborate unusual series' of oxindole alkaloids, such as horsfiline (9).

Medicinal Convolvulaceae



An interesting feature of the Convolvulaceae is their ability to elaborate LSD-like indole alkaloids. Both *Rivea corymbosa* (L.) Hall and *Ipomoea violacea* L., from which the Mexican magical drugs *ololiuqui* and *bado negro*, respectively, are prepared, contain a number of indoles related to the ergot alkaloids. D-Lysergic acid amide (ergine) is the major constituent of the seeds of both *Rivea corymbosa* and *Ipomoea violacea*. The seeds contain also small amounts of isowergine, chanoclavine, and elymoclavine.

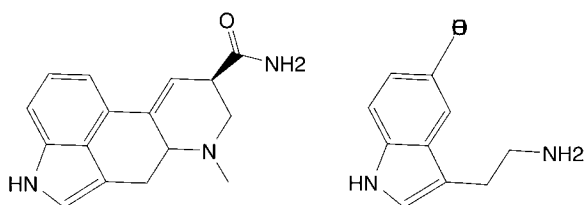


Chanoclavine

Elymoclavine

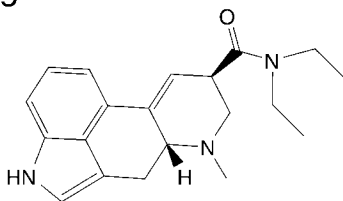
Drowsiness, apathy, and mental detachment seem to be the major effects of *ololiuqui*. The derivatives of lysergic acid present in *ololiuqui* are widely distributed throughout

the genus *Ipomoea* and other Convolvulaceae species. About 50 plant species from this family are used for medicinal purpose in Asia and the Pacific.

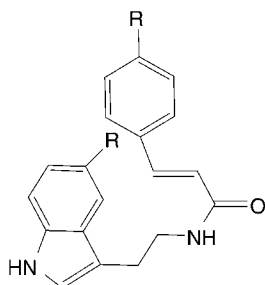


Ergine

Serotonin



Lysergic acid diethylamide



Macrolactam indole alkaloid

Ipomoea obscura (L.) Ker-Gawl., or obscure morning glory, is a slender climber common on fences. It is native to tropical East Africa, the Mascarene Islands, tropical Asia, throughout the Malay Archipelago, to northern Australia and Fiji. The leaves are cordate to 5 cm long and the flowers are infundibuliform and creamy white (Fig. 35).

In Indonesia, a paste of leaves is applied on sores, ulcers, hemorrhoids, and swellings. The seeds of *Ipomoea obscura* (L.) Ker-Gawl are known to contain unusual indole alkaloids including ipobscurines B-D, being unique structural types characterized as serotonin hydroxycinnamic acid amide-type conjugates with a second phenylpropanoid moiety forming an ether with the 5-OH position of the indole nucleus (10). It would be interesting to know whether or not these alkaloids hold some potential as promoters of serotonergic neurotransmission.

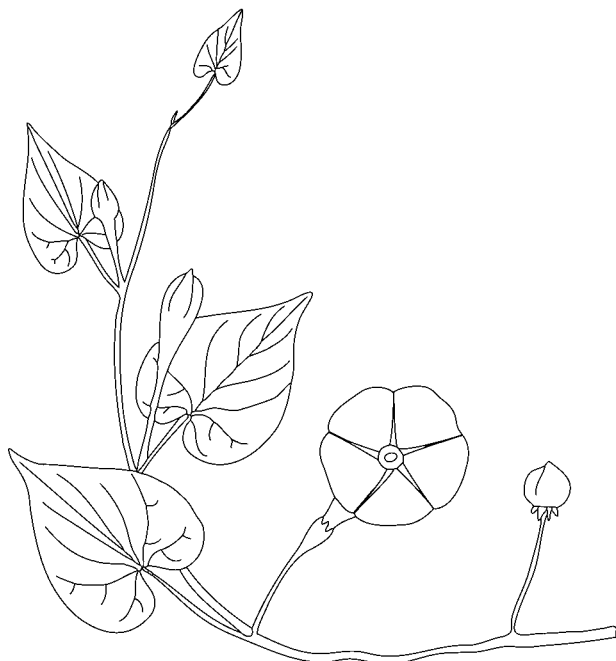


Fig. 35. *Ipomoea obscura* (L.) Ker-Gawl. Flora of Malaya. FRI No 27419. Geographical localization: Kuala Selangor, Malaysia November 10, 1983. Collector: F.S.B Ng. Botanical identification: F.S.B Ng, 4.2.1986.

***Ipomoea digitata* L.** (*Ipomoea paniculata* var. *digitata* Kuntze, *Quamoclit digitata* [L.] G. Don, *Convolvulus paniculatus* [Burm. f.] Kuntze, *Ipomoea paniculata* [L.] R. Br, *Ipomoea mauritiana* Jacq.), or alligator yam, *vidari*, *bhummy kushmanda* (Sanskrit), or *jari buaya* (Malay), is found in India and Southeast Asia. The plant is grown for ornamental purposes. The roots are ovoid, large, and tuberous. The leaves are large, palmately five to seven lobed, ovate, lanceolate, acute, or acuminate. The flowers are infundibuliform and purple and campanulate–infundibuliform. The fruits are small and ovoid capsules. There are four seeds in each fruit that are black and woolly (Fig. 36). In Cambodia, Laos, and Vietnam, the tubers are used to invigorate, stimulate venereal desire, prevent obesity, and moderate menses. In India, it is used as a general tonic, to treat diseases of the spleen and liver, for menorrhagia, debility, and fat accumulation. To date, the plant is unstudied for its potential as a source of neuroactive compounds.

Ipomoea indica (*Convolvulus indicus* J. Burman, *Ipomoea congesta* R. Brown), or ocean blue morning, glory, *koaliawa* (Hawaii), is a slender climber native to South America, and is cultivated and naturalized in coastal habitats and moist forests in several tropical countries including Indonesia, Malaysia, Burma, New Guinea, Philippines, Sri Lanka, and Pacific Islands. The leaves are cordate to 10 cm long. The flowers are infundibuliform, grow up to 7 cm long and 5 cm in diameter, and are deep blue in color (Fig. 37).



Fig. 36. *Ipomoea digitata* L. Forest Flora, Malay Peninsula. No 37918. Geographical localization: Peteni Hill, Kelantan, 10/16/1934. Collector: C.F. Symington.

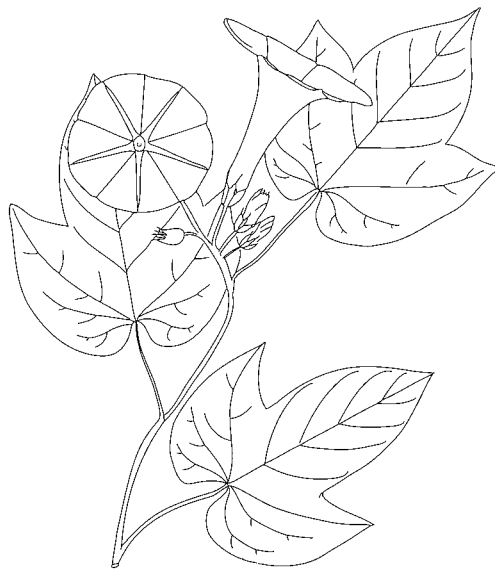


Fig. 37. *Ipomoea indica*. Forest Flora, Malay Peninsula. No 22249. Geographical localization: Gap Sanitarium garden, 1/20/1930. Collector: Symington. Botanical identification: 1958.

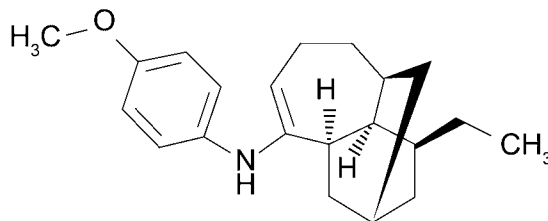
In Taiwan, the roots are used to relieve the bowels from costiveness. To date, the pharmacological potential of this plant is unknown.

Medicinal Apocynaceae

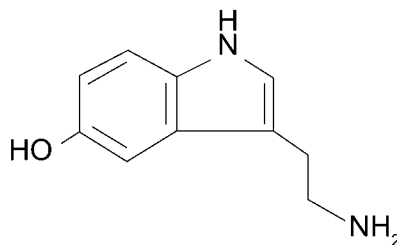


Perhaps no other family of flowering plants has aroused more interest in the field of pharmacological research than the Apocynaceae, the only family that abounds with indole alkaloids of proven clinical value. An interesting aspect in this field of neuropharmacological research is the fact that Apocynaceae elaborate Iboga alkaloids, which are present particularly in the genus *Tabernanthe*, and principally in a Central African shrub *Tabernanthe iboga*. The roots are chewed by the natives to offset hunger and fatigue, and large doses produce excitement, mental confusion, and a drunken madness characterized by prophetic utterances (11).

Tabernanthe iboga contains a series of alkaloids including Ibogaine and tabernantheine. Ibogaine was isolated in 1901, is like serotonin and harmine, and has attracted a great deal of interest on account of its capability to reduce drug craving. The mechanism underlying this effect may result from a regulator of the serotonergic system that, in turn, regulates dopamine release (12).



Ibogaine



Serotonin

Ibogaine protects the *N*-methyl-*D*-aspartate neuron receptors against excessive release of excitatory amino acids and represents, therefore, a potential therapeutic agent for the treatment of Alzheimer's disease, Huntington's chorea, and other

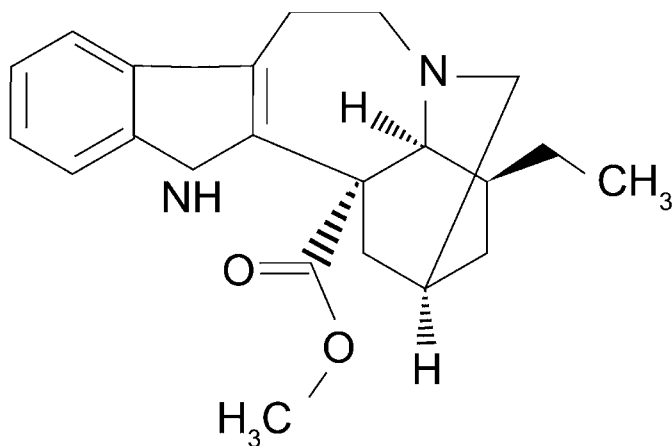


Fig. 38. *Ervatamia pandacaqui* (Poir.) Pichon. Flora of The Philippines. Herbarium Vadense (WAG). Botanical identification: A.J.M. Leuwenberg, 1987. Geographical localization: Pinamalayan, Mindanao. Field collector: Ramos. June, 1922.

brain diseases. The flora of tropical Asia is a rich source of Apocynaceae, including medicinal species, and represents therefore an exciting source of potentially serotonergic alkaloids for the treatment of depression. In this section, two species belonging to the genus *Ervatamia*, which is closely related to the genus *Tabernaemontana*, are described.

***Ervatamia pandacaqui* (Poir.) Pichon** (*Tabernaemontana cuminingiana* A. DC., *Tabernaemontana pandacaqui* Poir., *Tabernaemontana semperflorens* Perr., *Tabernaemontana thailandensis* P. T. Li.), or *ping mai gou ya hua* (Chinese) or *susun kepala* (Philippino), is a shrub that grows to a height of 4 m. The plant grows wild in China, Taiwan, Indonesia, Malaysia, the Philippines, Thailand; Australia, and the Pacific Islands. The leaves are decussate and elliptic. The corolla is white and salver-shaped, with five lobes obliquely oblong and falcate. The fruits are pairs of follicles obliquely ellipsoid (Fig. 38). In the Philippines, the plant is used to soothe bruises and swellings. A decoction of the root and bark is used to treat intestinal disorders and to treat the bites of poisonous animals.

A crude alkaloidal fraction from the stem of *Tabernaemontana pandacaqui* decreased the motor activity, respiratory rate, induced ataxia, antinociception, and loss of screen grip in rats, suggesting a CNS depression. The extract brought about the prolongation of pentobarbital sleeping time and the oxotremorine-induced salivation, hence possible cholinergic effects (13).



Coronaridine

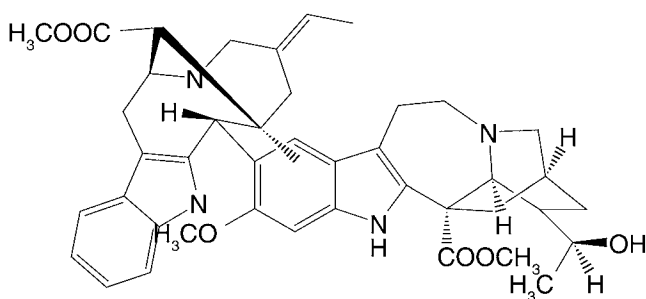
The active constituent involved here is currently unknown, but the plant is known to produce indole alkaloids including voacangine and coronaridine, which exhibited significant analgesic and hypothermic effects in mice at a dose of 25 mg/kg, orally (14,15). Because *Ervatamia pandacaqui* (Poir.) Pichon elaborates iboga alkaloids, such as ibogamine and tabernanthine, and congeners, such as coronaridine, could it be a source of serotonin re-uptake inhibitors (16)?

***Ervatamia corymbosa* (Roxb.) King & Gamble** (*Tabernaemontana corymbosa* Roxb. ex Wall, *Pagiantha peninsularis* Kerr, *Pagiantha peninsularis* var. *brevituba* Kerr, *Ervatamia chinensis* [Merrill] Tsiang, *Tabernaemontana chinensis* Merrill, *Tabernaemontana yunnanensis* [Tsiang] P. T. Li), or *san fang gou ya hua* (Chinese) or *pelir kambing* (Malay), is a shrub that grows to a height of 3 m tall in China, Indonesia, Laos, Malaysia, Burma, Thailand, and Vietnam. The leaves are decussate, papery, and acuminate at apex. The flowers are white, with five obliquely elliptic, mostly falcate lobes. The fruits are pairs of follicles obliquely ellipsoid (Fig. 39).

In China, the bark and leaves are used for the treatment of fractures. The roots are used in Malaysia to recover from childbirth and exhaustion, and a paste of the plant is used to treat orchitis. The plant contains indole alkaloids such as conodurinine, 19'(S) hydroxyconoduramin, 19'(S)-hydroxyervahanine A, and related iboga alkaloid congeners, and like the species mentioned earlier, and in fact the genera *Ervatamia*, in general, would be worth investigating for serotonergic activities (17).



Fig. 39. *Ervatamia corymbosa* (Roxb.) King & Gamble. Flora of Malaya. Field No 104429. Geographical localization: Krau Game Reserve, G. Benom, Central Pahang in primary forest hillside, altitude: 1000 feet. Field collector: S. Chelliah, 7/14/1967. Botanical identification: A.J.M Leeuwenberg, 1986. Herbarium Vadense.

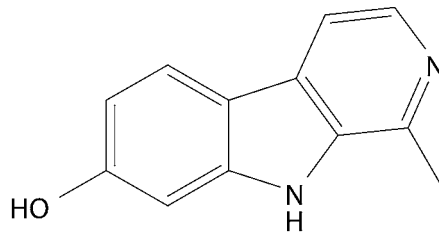


19' (S) hydroxyconoduramine

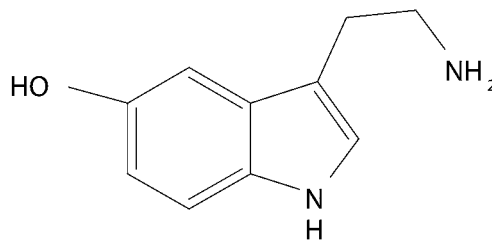
Medicinal Zygophyllaceae

The family Zygophyllaceae is made up of 30 genera and 250 species of shrubs known to have the tendency to elaborate a series of serotonin-like psychedelic indole alkaloids such as harmine, harmol, and harmaline, notably found in the seeds of a medicinal

plant that grows in the arid regions northern Africa to northern India and Manchuria, *Peganum harmala* L., or Turkey red or Syrian rue (peganum, *British Pharmaceutical Codex*, 1934). The seeds have been used to induce a psychic excitement comprising of visual distortions that are similar to those induced by LSD.

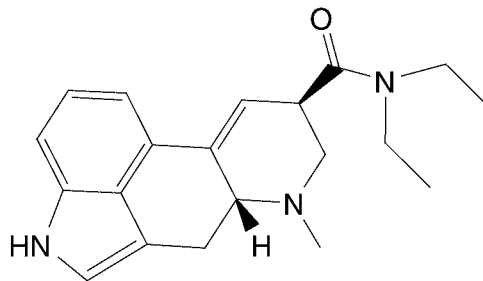


Harmol



Serotonine

Note that the Malpighiaceae and Zygophyllaceae belong to the orders Polygalales and Sapindales, respectively, with both orders being quite close to the Rosidae, hence the probability of finding such alkaloids near to and in these orders. This type of indole alkaloids, or “harmala alkaloids,” are identical to those of *ayahuasca* made from the *Banisteriopsis* species in the Malpighiaceae.



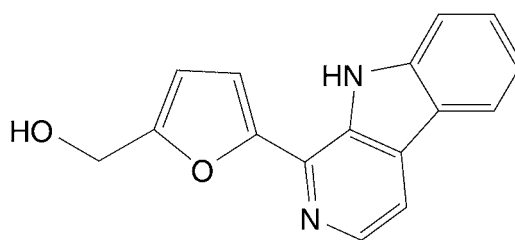
LSD

Tribulus terrestris L. (*Pedaliium murex*), or ground burnut, puncture vine, *txu*, *chih hsing*, *tu chi li* (Chinese), is an annual, prostrate dwarf shrubby herb that grows to a height of 60 cm. The plant grows in disturbed areas, roadsides, railways, cultivated



Fig. 40. *Tribulus terrestris* L.

fields, and abandoned gardens in Europe, the United States, and the Asia–Pacific region. The stems are terete, pilose, minute, and green to reddish-brown, and produce numerous stout burrs that can injure people and animals and puncture bicycle tires. The leaves are opposite and pinnate (Fig. 40). In China, the seeds are used as diuretic, tonic, abortifacient, galactagogue, and an alternative anthelmintic. The flowers are used to treat leprosy and a decoction is used to treat skin diseases. The activity of the plant as male aphrodisiac as been demonstrated experimentally in rodents (18).



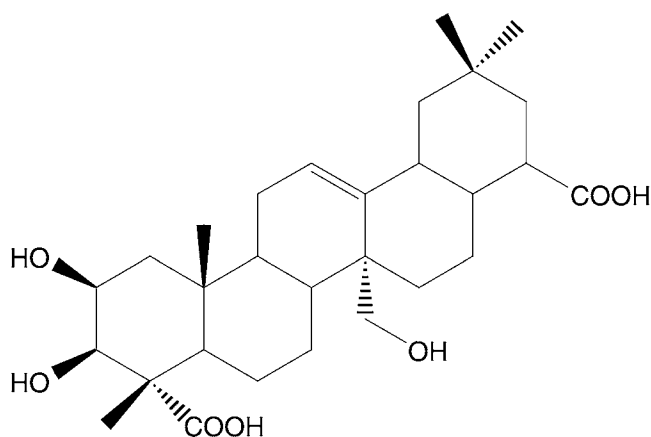
Perlolyrine

The plant is known to elaborate a β -carboline alkaloid, such as tribulusterine, shown by synthesis and spectroscopic analysis to be the (5-hydroxymethyl)-2-furyl analog perlolyrine (19,20). An interesting development from this observation would be to assess the serotonergic activity of perlolyrine. One might suppose that the diuretic property mentioned previously might involve some levels of serotonergic activity

because serotonin re-uptake has been associated with the development of severe hyponatremia (21). Note that perlolyrine is present in several members of the Polygalaceae family.

Medicinal Polygalaceae

The family Polygalaceae consists of 10 families and 750 species of herbs, shrubs, or woody climbers that have attracted a great deal of interest on account of their ability to produce a series of neuroactive oleanane saponins known as polygalasaponins. In addition, Polygalaceae, like the Malpighiaceae, are member of the Polygalales and elaborate also a series of indole alkaloids that are of neuropharmacological interest. In Asia and the Pacific, about 10 species of plants classified within the family Polygalaceae are of medicinal value. Note that these plants are often used to counteract putrefaction, to treat cough, asthma, and bronchitis, to promote fertility, and to treat cerebral dysfunctions.



Polygalasaponin aglycone

Polygala tenuifolia (*Polygala sibirica*), or slender lobe milkwort, *yuan chih*, *yao jao*, *hsiao ts'ao* (Chinese), is a very slender perennial herb that grows to a height of 20 cm on sun-exposed hillsides, roadsides, and stony slopes of Korea, China, and Mongolia. The leaves are linear and the flowers are whitish (Fig. 41).

In China, the plant is known to promote mental powers. It is used to treat cough, jaundice, hysteria, convulsions, mammary abscess, and gonorrhea. The leaves are used for sperm leaking. The roots and leaves are used to promote urination. In Cambodia, Laos, and Vietnam the roots are used to calm and to treat cough. In Korea, the plant is used to treat psychotic illnesses. In vitro binding studies suggested a potential mechanism for its antipsychotic action, as saponins known as polygalasaponins bind to both dopamine and serotonin receptors. Polygalasaponins (25–500 mg/kg) showed receptor antagonist properties, and their possible utility as antipsychotic agents has been subjected (22). It would be interesting to know whether further study on the precise molecular activity of polygalasaponin discloses any original molecular pathways in the

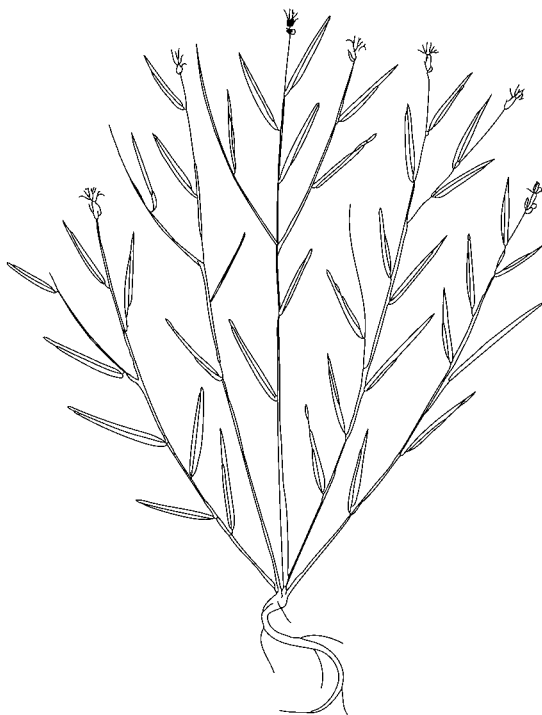


Fig. 41. *Polygala tenuifolia*.

search for serotonin re-uptake inhibitors. Because saponins are very polar, how could it cross the hemato-encephalic barrier and reach the brain unless injected intracranially? Is the genin instead neuroactive?

Note that the plant elaborates a series of carboline alkaloids including 1-carbobutoxy- β -carboline, N9-formylharman, 1-carboethoxy- β -carboline, 1-carbomethoxy- β -carboline, perlolyrine, harman, and norharman (23). An interesting development would be to assess these alkaloids for central nervous activity.

***Polygala japonica* Houtt.** (*Polygala sibirica* non L.), or dwarf milkwort, *himehagi* (Japanese), is a little perennial herb of Australasia. The leaves are tiny and broadly elliptic, and the flowers are purplish-blue (Fig. 42).

It is medicinally used from Korea to Cambodia, Laos, and Vietnam. In Korea, the plant is used as an aphrodisiac for males and the elderly. In Japan, a decoction of the root is drunk to treat cough, invigorate, and treat tuberculosis. In Taiwan, the plant is an external remedy for snake bites. In Cambodia, Laos, and Vietnam, the roots are used to treat bronchitis, amnesia, and to stimulate memory and urination. The antitussive property is very probably owed to polygalasaponins, which are known to abound in the plant (24–26). It would be interesting to know whether the tonic properties mentioned here are owed to serotonergic mechanisms. What is the alkaloidal content of this herb?

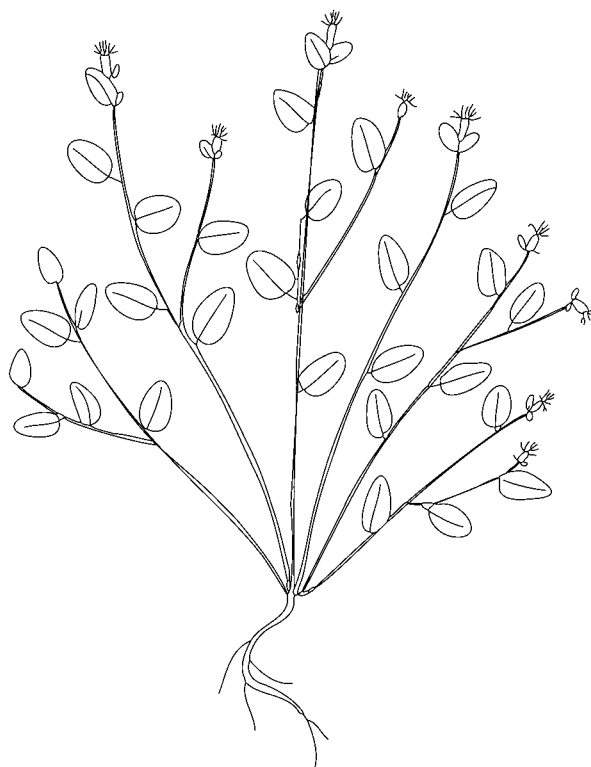
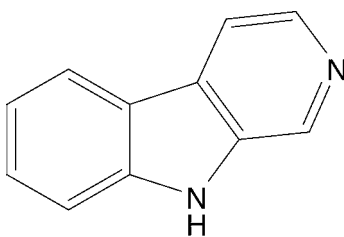
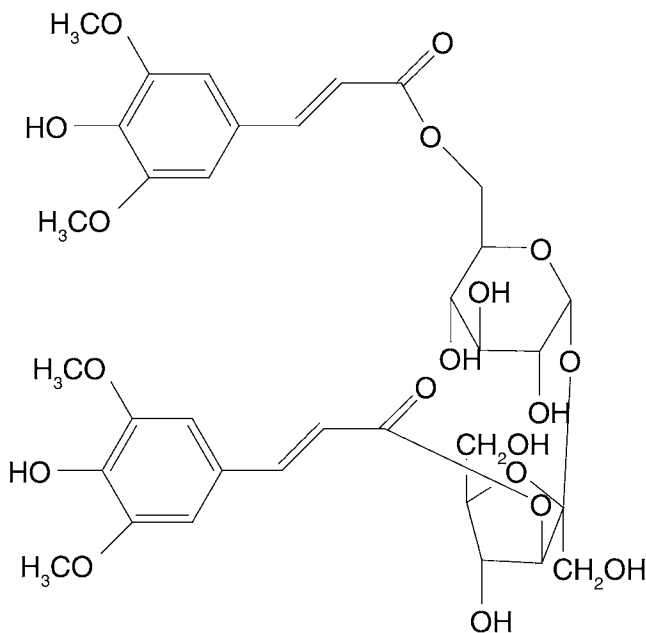


Fig. 42. *Polygala japonica*.



Norharman

***Polygala glomerata* Lour.** (*Polygala chinensis* L., *Polygala densiflora* Blume, *Polygala glomerata* Lour. var. *pygmaea* C.Y. Wu & S.K. Chen, *Polygala glomerata* Lour. var. *villosa* C.Y. Wu & S.K. Chen, *Polygala subopposita* S.K. Chen), or *hua nan yuan zhi* (Chinese), is an annual herb that grows to a height of 25 cm in grasslands, shrub forests, and on slopes of hills in China, Taiwan, India, Bhutan, Cambodia, Indonesia, Laos, Malaya, New Guinea, Philippines, Thailand, and Vietnam. The leaves are obovate, elliptic, or lanceolate. The flowers are 4.5 mm long, yellowish, or white with pink. The fruits are globose, 2 mm in diameter, narrowly winged capsules.

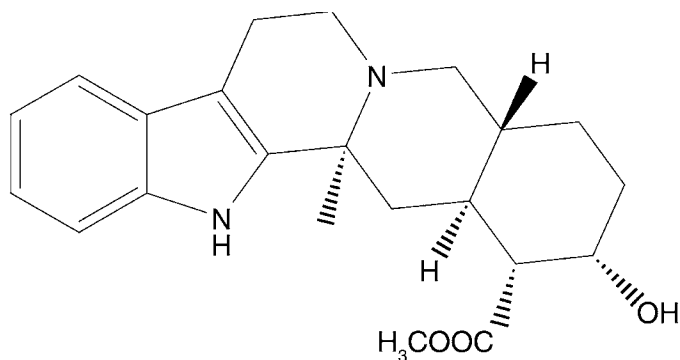
Oligosaccharides of *Polygala glomerata*

In Vietnam, Cambodia, and Laos, the roots are used to cure inflamed throat, reduce fever, and remove blood from urine. In Indonesia, a tea of the leaves is drunk to treat asthma and cough. The plant is known to elaborate a series of polygalasaponins including polygalasaponins XLII–XLVI, hence mucolytic properties (26,27). The plant elaborates a series of oligosaccharide polyesters, the effects of which would be worth assessment because oligosaccharides, especially from the Caryophyllidae, displayed very encouraging pharmacological potentials as antiviral and immunomodulatory agents.

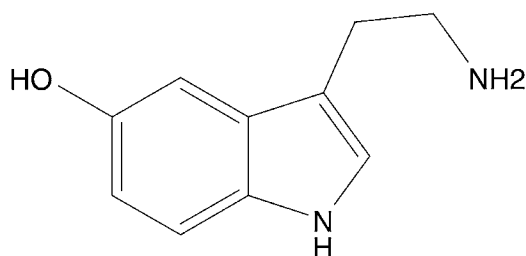
Medicinal Rubiaceae



The family Rubiaceae consists of about 450 genera and 6500 species of tropical and sub-tropical trees, shrubs, and climbers that can be quite easily recognized in field collection by their leaves, which are opposite and stipulate, the stipule being interpetiolar. *Cephaelis*, *Nauclea*, *Cinchona*, *Mitragyna*, *Corynanthe*, *Pausinystalia*, *Uncaria*, *Pogonopus*, and *Remijia* species are of particular interest in the family because they produce monoterpene indole and quinoline alkaloids, some of which are used as therapeutic alkaloids, such as quinine and emetine. Yohimbine occurs in the genera *Pseudocinchona* and *Yohimbe*. In human subjects, yohimbine at 0.5 mg/kg produces a psychic state stimulating considerable anxiety with tenseness, restlessness, irritability, and schizophrenic psychosis.



Yohimbine



Serotonin

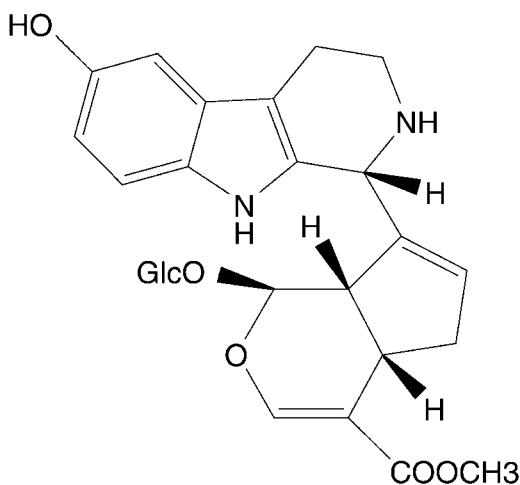


About 120 species of plants classified within the family Rubiaceae are used in traditional medicine of Asia and the Pacific, of which, *Mitragyna speciosa* has been used throughout Southeast Asia, especially in Thailand and Borneo, as an intoxicant. The leaves are chewed alone or mixed with betel, or else prepared for smoking like opium, and its use is legally prescribed in Thailand.

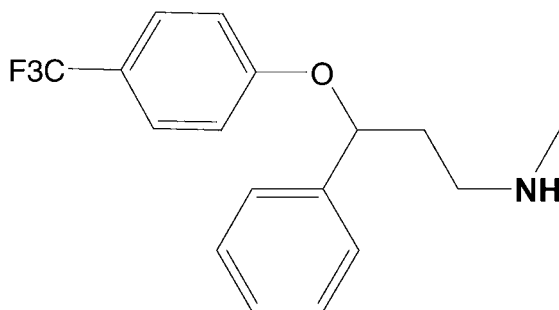
The discovery of natural products of therapeutic value, and especially serotonergic agents, from this very large family is most probable.

A classical example of medicinal Rubiaceae of Asian origin is *Uncaria gambir* (Hunter) Roxb., from which is extracted an astringent extract (catechu, *British Pharmaceutical Codex*, 1963), employed for the treatment of diarrhea.

***Psychotria adenophylla* Wall.** (*Psychotria siamensis* Ridl.) is a shrub that grows wild to a height of 1 m in Northeast India, Vietnam, Cambodia, Laos, Malaysia, and Java. The leaves are simple, decussate, and stipulate, and show 15 pairs of secondary nerves. The inflorescences are racemose. The flowers are small and tubular. The fruits are globose, glossy, and yellowish. In Vietnam, Cambodia, and Laos, the plant is used to treat maladies of the chest.



Umbellatine



Fluoxetine (Prozac®)

To date, some evidence has already been presented that suggests the genera *Psychotria* to hold potentials as a source of serotonergic agents. Both et al. drew attention to the fact that psychollatine, an indole alkaloid isolated from Brazilian *Psychotria umbellata*, is centrally active via serotonergic 5-HT₂ (A/C) receptors (28). In experimental models of anxiety, diazepam (0.75 mg/kg) and psychollatine (7.5 and 15 mg/kg) showed anxiolytic-like effects at doses that do not increase sleeping time nor alter spontaneous locomotor activity. The anxiolytic effect of psychollatine was prevented by ritanserin, indicating the mediation of 5-HT₂ receptors. In the forced swimming model of depression, psychollatine (3 and 7.5 mg/kg) effects were comparable to the antidepressant fluoxetine, or Prozac® (205 mg/kg). Investigating the medicinal flora of the Pacific Rim, and especially the *Psychotria* species, might possibly result in the characterization of antidepressants of clinical value.

Rubia cordifolia (*Rubia cordifolia* var. *mungista* [Roxb.] Miq, *Rubia cordifolia* var. *stenophylla* Franch, *Rubia akane* Nak.), or Indian madder, Bengal Madder, *ch'ien ts'ao*, *ti hsueh*, *jan fei ts'ao*, *hsueh chien-ch'ou*. (Chinese), *munjette*, *mandjuchaka* (Sanskrit), *guo*

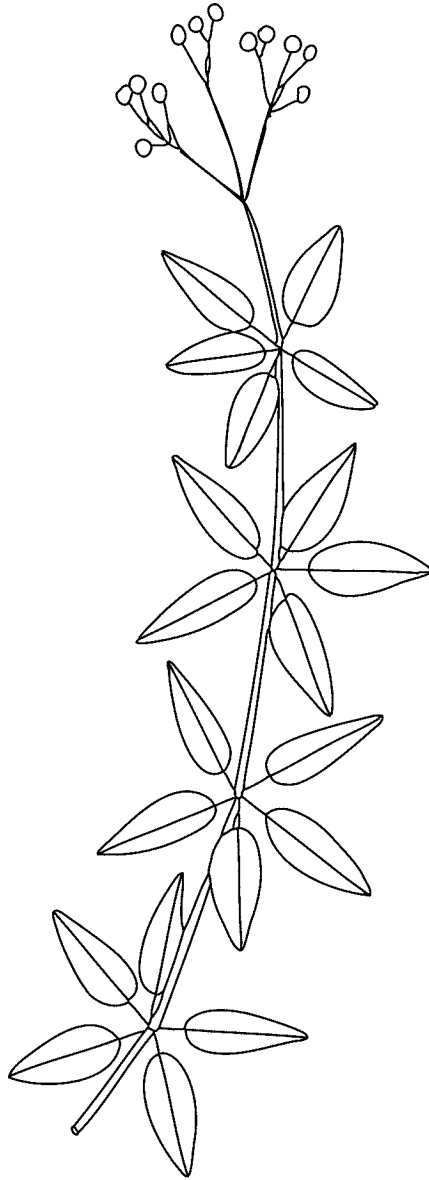
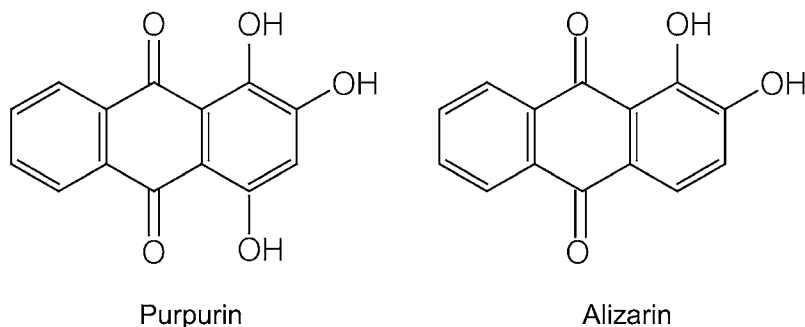


Fig. 43. *Rubia cordifolia* L.

shan long (Taiwan), or *nihon akane*. (Japanese), is a perennial creeping or climbing herb that grows to a length of 3 m in the Himalayas (up to 2000 m), Japan, and China. The stem is quadrangular and minutely prickly. The leaves are cordate and in whorls of four to five (Fig. 43). The plant abounds with purpurin, an anthraquinone, and is used for dyeing a deep red color in China, Tibet, and Japan (29).



In China and Tibet, the plant is held in great esteem. It was believed that the color of the plant was caused by transformed human blood. The root is used to treat rheumatism, jaundice, hemorrhages, and all sorts of exhausting discharges. In Korea, the root is used to treat rheumatism, jaundice and menstrual disorders. In the Philippines, a decoction of roots is drunk as a remedy for urinary disorders. One might have observed the obvious relationship between the red color of the sap and the blood-related medicinal uses of the plant; it illustrates the “doctrine of signatures” of Paracelsus.

In regard to the experimental evidence available, a substantial number of reports on the chemical constituents of the plant are available, but much less work has been done with the pharmacological properties. Kasture et al., however, made the important observation that a triterpene isolated from *R. cordifolia* induces anxiety in rodents, an effect accompanied with an increase in serotonin contents in the brain (30). An interesting development from that observation would be to explore further the molecular-pharmacological pathway and the effect of this agent on the serotonergic system because terpenes, compared with indole alkaloids, are seldom reported for serotonergic activities.

***Uncaria rhynchophylla* Miq.** (*Ourouparia rhynchophylla* Matsum.), or Chinese cat’s claw; *kou t’eng*, or *tiao t’eng* (Chinese). The plant is a woody climber native to China and Japan. The stem is quadrangular, hollowed, and regularly hooked. The leaves are simple, opposite, and stipulate, with the stipules being interpetiolar. The inflorescences are globose on long pedicels on leaf axis (Fig. 44). In China, sundried pieces of hook-bearing stems are used to reduce fever in children and treat nervous disorders of children. In adults, the plant is used to treat dizziness, moles in vision, and bilious disorders. Hou proposed two phenolic compounds—catechin and epicatechin—to be involved in the neurological properties of *Uncaria rhynchophylla* because these molecules inhibited the enzymatic activity of monoamine oxidase-B with inhibiting concentration (IC)₅₀ values of 88.6 and 58.9 μM in vitro (31). Can we reasonably expect phenolic compounds to exert significant CNS activity?

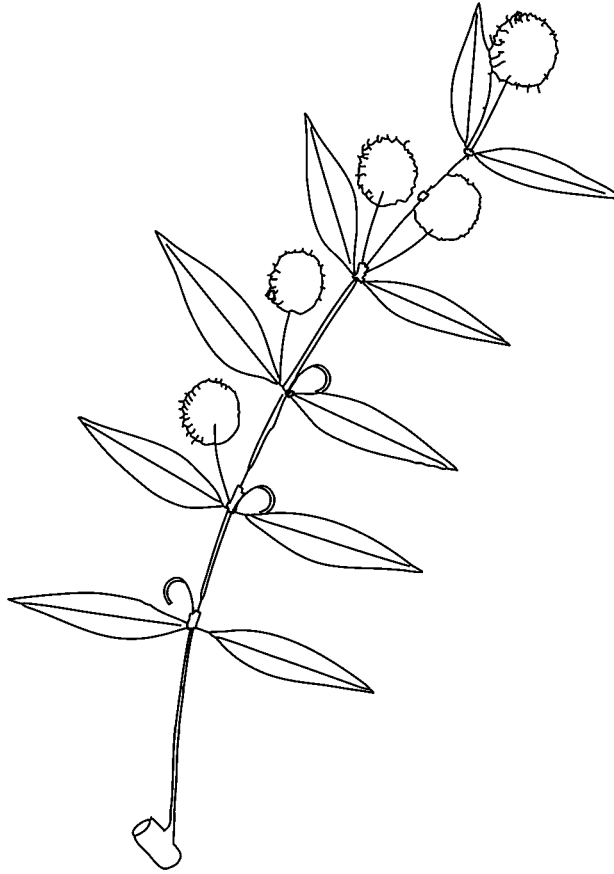
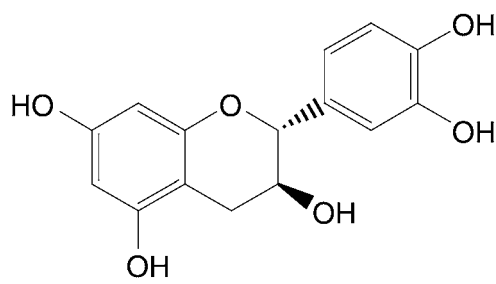
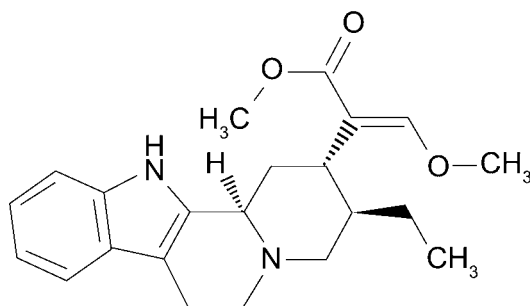


Fig. 44. *Uncaria rynchophylla* Miq.



(+) – Catechin

The most likely explanation for these results is that simple phenolics inhibit a very large array of enzymes *in vitro*. The most likely explanation for the CNS effects of *Uncaria rynchophylla* would be that indole alkaloids, such as dihydrocorynantheine or hirsutine (32), interact with the central neurotransmission and possibly the serotonergic system.



Hirsutine

Evidence in favor of such a hypothesis is given by Jurgensen et al. who have first reported the fact that an alkaloid fraction from *Uncaria tomentosa* (Willd.) DC, a vine used by Peruvian Indians to treat several diseases, given by the intraperitoneal route, dose-dependently suppressed the behavioral response to the chemical stimuli in the models indicated and increased latencies in the thermal stimuli models (33).

The antinociception caused by the fraction in the formalin test was significantly attenuated by intraperitoneal injection of mice with ketanserin (5-HT₂ receptor antagonist), but was not affected by naltrexone (opioid receptor antagonist), atropine (a nonselective muscarinic antagonist), L-arginine (precursor of nitric oxide), prazosin (α₁-adrenoceptor antagonist), yohimbine (α₂-adrenoceptor antagonist), and reserpine (a natural monoamine depletory alkaloid from *Rauwolfia serpentina* [Rubiaceae]). Together, these results indicate that the fraction abrogates, dose-dependently, pain via interaction with 5-HT₂ receptors.

PLANTS AFFECTING THE GABA_AERGIC NEUROTRANSMISSION

γ-Aminobutyric acid (GABA) is an inhibitory neurotransmitter in the CNS. Neurons using the GABA as neurotransmitter are among the most abundant in the CNS. GABAergic neurones occur mainly as local neurons or interneurons present in all area of the CNS involved in the local modulation of neuron activity and to a lesser extent, as projecting or principal neurones (cerebellar Purkinje cells, striatonigral, striathothalamic, and nigrothalamic pathways). There may be five or more types of GABA receptors, but GABA receptors GABA_A and GABA_B are the most studied. GABA_A receptor blockers, such as bicuculline and picrotoxin, are both GABA_A receptor-blocking agents that impede the GABAergic presynaptic inhibition of excitatory transmission of primary afferent neurones of the spinal cord, hence a general increase in neuronal activity, alertness, anxiety, spasms, seizures, and even death (Fig. 45).

Picrotoxinin is a sesquiterpene, which is found notably in the seeds *Anamirta paniculata* Coleb. (levant berries, Menispermaceae; Fig. 46). This substance is toxic, and as little as 20 mg induces epileptiform convulsions, myosis, and dyspnea with more or less

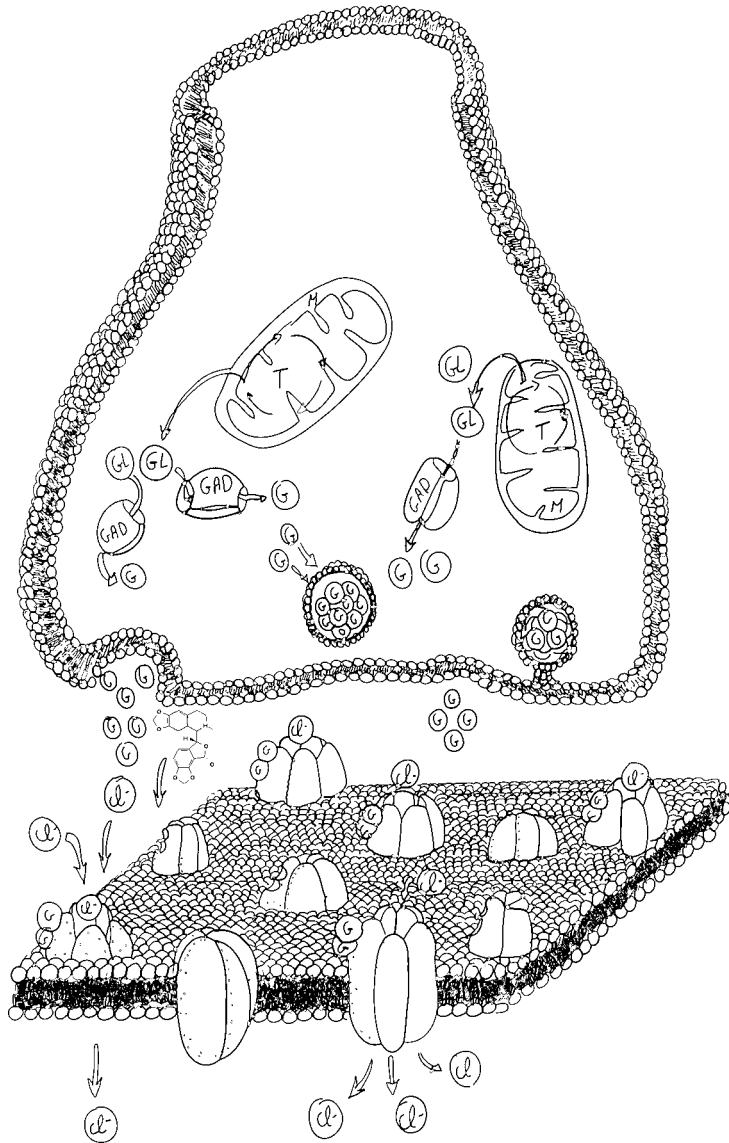


Fig. 45. GABAergic neurone synapse. GAD, glutamic acid decarboxylase; M, mitochondria; G, GABA.

prolonged apnea. Picrotoxin (*British Pharmacopoeia*, 1963) has been used in the treatment of barbiturate poisoning (3–6 mg, intravenously) in Western medicine. Both compounds are elaborated in the Magnoliidae (Ranunculales and Papaverales).

Bicuculline is an isoquinoline alkaloid elaborated from members of the family Fumariaceae (Papaverales), especially in *Corydalis*, *Dicentra*, and *Fumaria* species. Bicuculline, like picrotoxin, is a specific GABA receptor-blocking agent that impedes the

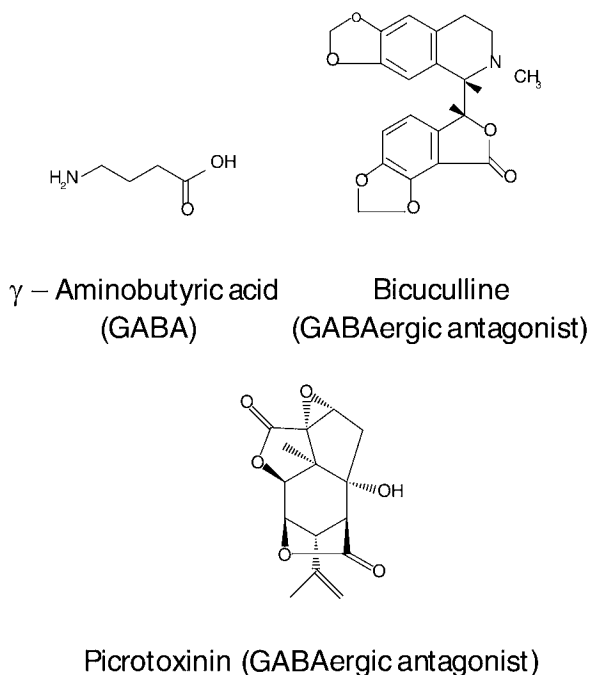


Fig. 46. Examples of GABAergic natural products from flowering plants.

GABAergic presynaptic inhibition of excitatory transmission of primary afferent neurones of the spinal cord resulting in epileptiform convulsions, myosis, and dyspnea with more or less prolonged apnea.

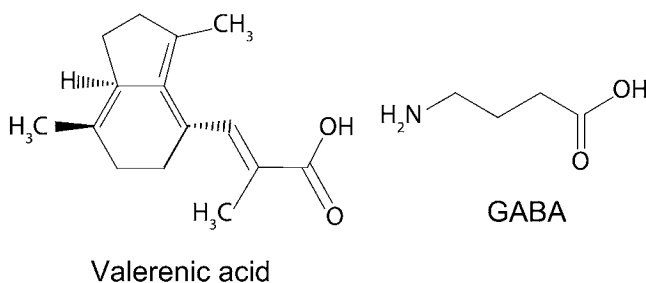
One of the most spectacular applications in this field is the development of a GABA_A receptor agonist: the benzodiazepine. About 15 types of benzodiazepine derivatives are currently available in the United States and marketed as sedatives, anxiolytics, muscle relaxants, intravenous anesthetics, and anticonvulsants. Anxiolytics known as benzodiazepines, which bind to a very specific region of GABA_A receptors. However, benzodiazepines are sedatives that induce serious memory impairment, drowsiness, and dependence, and there is a need for agents with lighter side effects. Experimental observations have led to the suggestion that the etiology of Huntington's chorea, epilepsy, and Alzheimer's disease could be linked to the GABAergic system. The search for GABA_A agonists appears, therefore, as a very exiting quest, and one looking for such agent might look into the medicinal flora of the Asia-Pacific region.

A classic example of a medicinal plant of Asia and the Pacific with GABAergic properties is *Piper methysticum* Forst. (Kava, *British Pharmaceutical Codex*, 1934), or *kava-kava*, the rhizomes of which have been used since a very early period of time by Polynesians to allay anxiety and reduce fatigue. Kava has been marketed in Europe to treat sleep disorders and anxiety. The beverage normally induces a form of euphoria, described as a happy state of complete comfort and peace, with ease of conversation

and increased perceptivity, followed by muscular fatigue and restful sleep. Klohs et al. identified the active constituents as series of α -pyrone including kawaine, which mediates anxiolytic effects through GABA_A receptor binding (34,35).

Medicinal Valerianaceae

Valeriana officinalis has been used in traditional medicine for its sedative, hypnotic, and anticonvulsant effects. There are several reports in the literature supporting a GABAergic mechanism of action for valerian. Valerian (*British Pharmaceutical Codex*, 1963) consists of the dried rhizome or roots of *Valeriana officinalis* containing not less than 18% alcohol (60%)-soluble extractive. It has been used in the form of infusion, tinctures (1 in 8 prepared by maceration in alcohol [60%]; dose 4–8 mL, Tinct. Valerian Simp, *British Pharmaceutical Codex*, 1949) to calm. Some evidence has already been presented that indicates that the anxiolytic and sedative effects of valerian involve the GABAergic system. In vitro, the aqueous and hydroalcoholic extracts of *Valeriana officinalis* L. displace [³H]muscimol from GABA_A receptor (36,37). Yuan et al. made the important observation that valerian extract (3 mg/mL) and valerenic acid (100 μ M) inhibit the firing rate in most brainstem neurons with IC₅₀ values of 240 mg/mL and 23 mM, respectively (37). Bicuculline antagonized the inhibitory effects of both the valerian extract and valerenic acid.



The rhizomes and roots of *Valeriana wallichii* DC. contain 6-methylapigenin, which is a competitive ligand for GABA_A receptor (38). In the Asia–Pacific region, *Nardostachys chinensis* L., *Nardostachys jatamansis* DC., *Patrinia scabiosaefolia* Link, *Valeriana officinalis* L., *Valeriana dageletiana* Nak. ex Maekawa, and *Valeriana hardwickii* Wall. are used as alternative remedies.

Nardostachys chinensis L. is an herb that grows to a height of 50 cm. The stem is erect and develops from an aromatic rhizome. The leaves are linear and somewhat spatulate. The flowers are small, tubular, and packed in a terminal cyme (Fig. 47). In China, the rhizome is used to treat swollen ankles, assuage toothache, and is given for congested chest and stomach. The plant is interesting because it elaborates a sesquiterpene known as nardosinone, which is an enhancer of the neuritogenic action of dibutyryl cyclic (dbc)AMP and staurosporine, hence the potential as a pharmacological tool for studying the mechanism of action of neuritogenic substances. Nardosinone enhances staurosporine- or dbcAMP-induced neurite growth from PC12D cells in a



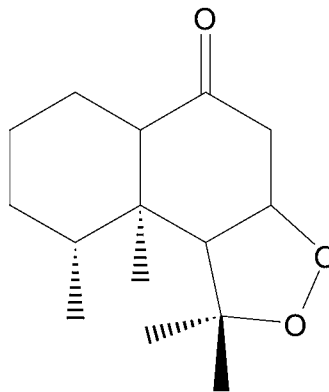
Fig. 47. *Nardostachys chinensis* L.

concentration-dependent manner, possibly by amplifying both the mitogen-activated protein (MAP) kinase-dependent and -independent signaling pathways of dbcAMP and staurosporine. Nardosinone stimulates a downstream step of MAP kinase in the MAP kinase-dependent signaling pathway (39). Note that the pharmacological potentials of this plant for GABAergic properties are unexplored.

***Nardostachys jatamansi* DC.** (*Nardostachys grandiflora* DC.), or spikenard, *jatamansi* (Sanskrit), *jatamansi* (Hindi), *jatamanshi* (Malayalam), *jatamashi* (Tamil); *kan sung shiang* or *ku mi che* (Chinese), is a perennial herb that grows to a height of 60 cm in the Himalayas (from 3000 to 5000 m), Punjab, and Bhutan. The stem is erect, pubescent, and develops from an aromatic rhizome. The flowers are pinkish-blue and arranged in terminal globose cymes (Fig. 48).



Fig. 48. *Nardostachys jatamansi* DC.



Nardosinone

In China, the rhizome is used as a deodorant, carminative, and stimulant. A decoction is used in various skin affections and in the bath to give fragrance to the body. In India, the rhizome is used to treat depression, hysteria, epilepsy, convulsions, headache, colic, and as a tonic and carminative.

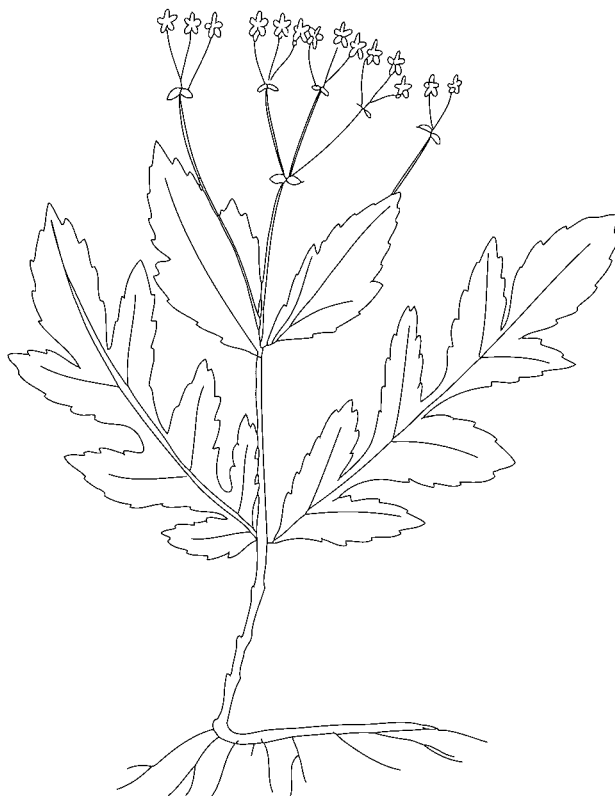


Fig. 49. *Patrinia scabiosaefolia* Link.

The plant has been shown to possess GABAergic properties. Prabhu et al. showed that acute and subchronic administration of an alcoholic extract of the roots of *Nardostachys jatamansi* to male albino Wistar rats resulted in a significant increase in GABA (40). In addition, 2 weeks' oral pretreatment with the plant at a dose of 250 mg/kg abrogated alternations induced by ischemia, including neuronal cell death following middle cerebral artery occlusion (41). Note that the plant exhibits hepatoprotective effects (42). It would be interesting to learn whether further study on this herb discloses any original agent with GABAergic potentials.

***Patrinia scabiosaefolia* Link**, or *patrinia*, *ominameshi* (Japanese), *pai chang*, *ku chih*, *ku tu*, or *hai sho* (Chinese), is an erect herb that grows to a height of 1 m in East Asia and in sunny, grassy places in hills and mountains all over Japan. The root of this plant smells like spoiled soy. The leaves are fleshy, soft, whorled, dentate, and serrate. The flowers are small, yellowish-white, and arranged in corymbose cymes (Fig. 49).

The roots are used as an astringent, resolving anodyne and antidotal. It is also used to heal abscesses, assuage postpartum pain, and remove parasites from the skin. The plant was mentioned by Schimmel in the *American Journal of Pharmacy* in 1889. Clinical observation and pharmacological investigation of the sedative and hypnotic effects of the Chinese drug rhizome and root of *Patrinia scabiosaefolia* are discussed by Luo (43).

Note that the plant is known to abound with triterpenoid saponins (44,45). Is the plant holding GABAergic activity? One wonders.

Medicinal Lamiaceae

There is an increasing body of evidence to suggest that flavonoids and diterpenes of Lamiaceae might be of value as source of original antagonists of the GABAergic neurotransmission. Flavonoids in particular possess partial allosteric modulatory action at the GABA_A receptor complex and, therefore, constitute a possibly promising group of naturally occurring agents for the treatment of anxiety disorders. Huen et al. made the interesting discovery that 2'-hydroxyl substitution is a critical moiety on flavonoids with regard to benzodiazepine receptor affinities. Benzodiazepine receptor binding assay-guided fractionation of the methanol extract from sage leaves (*Salvia officinalis* L.), for instance, revealed flavones and abietane diterpenes functioning as benzodiazepine receptor-active components. Apigenin, hispidulin, and cirsimaritin competitively inhibit the binding of 3H-flumazenil to the benzodiazepine receptor with respective IC₅₀ values of 30, 1.3, and 350 μM (46,47).

The medicinal Lamiaceae, with about 250 species, represents a vast source of material to explore when looking for anxiolytic agents of clinical value. Among these medicinal species are *Scutellaria baicalensis* Georgi and *Leonotis nepetifolia*, the properties of which are described here.

***Scutellaria baicalensis* Georgi** (*Scutellaria micrantha* Fisch, *Scutellaria lanceolaria* Miq.), or Baical scullcap, Chinese scullap, or *huang ch'in* (Chinese), is a perennial herb that grows from a rhizome to a height of 1.20 m. It is common on sunny, grassy slopes, waste and cultivated areas, from 100 to 2000 m in China, Japan, Korea, Mongolia, and the steppes of Siberia. The stems are erect, much branched, quadrangular, and puberulent. The leaves are simple, decussate, and linear-lanceolate. The inflorescences are terminal racemes of up to 15 cm long. The flowers are tubular, labiate, dark blue, purple-red to blue, and up to 3 cm long (Fig. 50).

The drug consists of the roots, usually cut into slices is used to promote urination, to quiet pregnant uterus, stimulate respiratory organs, reduce fever, treat jaundice, diarrhea, cancer of the breast, and heal boils. In Korea, the plant is used to treat bacterial infection of respiratory and gastrointestinal tracts and fever. The plant has attracted a great deal of interest as it elaborates a series of flavones: baicalein, wogonin, and oroxylin, which bind antagonistically to the benzodiazepine binding site GABA_A receptor (48–50).

5,7-Dihydroxy-6-methoxyflavone (oroxylin A) inhibits the binding of [³H]flunitrazepam to rat cerebral cortical membrane with a IC₅₀ value of 1.09 μM. oral administration of oroxylin A (3.75–60 mg/kg) attenuated the anxiolytic, myorelaxant, and motor incoordination elicited by diazepam. Oroxylin A or wogonin given orally to animals (7.5–30 mg/kg) is anxiolytic similarly to diazepam (Valium®) through positive allosteric modulation of the GABA_A receptor complex via interaction at the benzodiazepine site (Fig. 51).

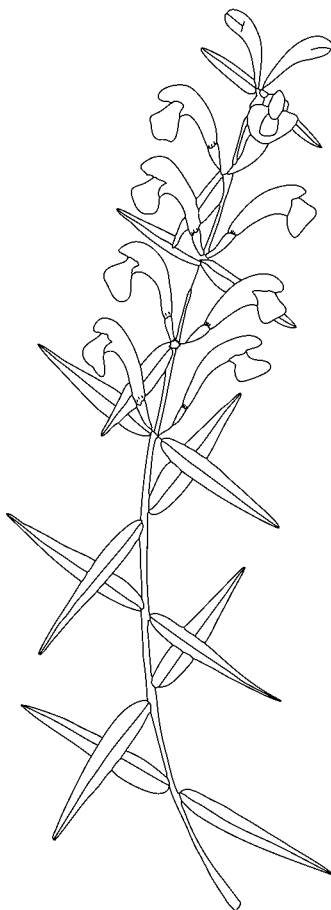
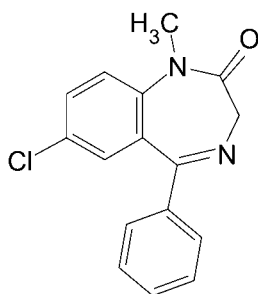


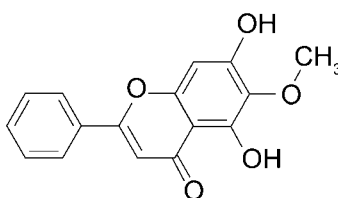
Fig. 50. *Scutellaria baicalensis* Georgi.

It is interesting to note that GABA and glutamine have been characterized from extracts of *Scutellaria lateriflora* L. (American skullcap) at 1.6 and 31 mg/g, respectively (51).

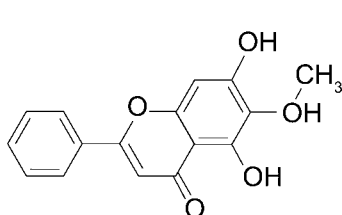
***Leonotis nepetifolia* R.Br.**, or annual lion's ear, is an annual herb that grows to a height of 2 m. The plant is native to Africa and is commonly grown as an ornamental. The stems are quadrangular. The leaves simple, decussate, and up to 12 cm long. The internodes are 20 cm long. The inflorescences are axillary, globular, and spiny (Fig. 52). The flowers are tubular, red, and about 2.5 cm long. In Malaysia, a paste of leaves is applied to wounds. The neuropharmacological potential of this plant is unexplored. Note that an aqueous extract of *Leonotis leonurus* in the doses of 200 and 400 mg/kg, respectively, abrogated the onset of tonic seizures produced by picrotoxin, hence some GABAergic activities (52). Aqueous extracts of the plant showed some levels of activity on guinea pig smooth muscle and rat cardiac muscle (53). Is 4,6,7-trimethoxy-5-methylchromen-2-one involved here (54)? An interesting development from these observations is the fact that flavonoids bind to GABA_A receptors.



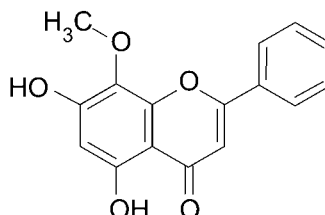
Diazepam (Valiumfi)



Oroxylin A



Baicalein



Wogonin

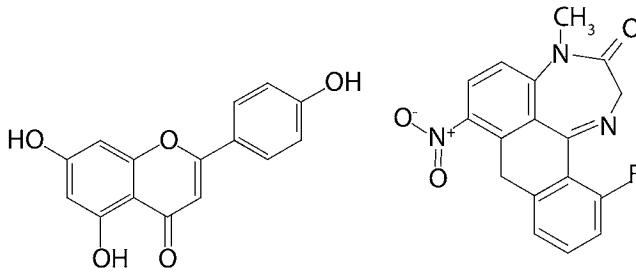
Fig. 51. Valium® and GABAergic flavonoids of *Scutellaria baicalensis* Georgi.

Medicinal Asteraceae

A remarkable advance in the neuropharmacological properties of Asteraceae has been provided by Viola et al. and Avallone et al. (55,56). They made the important observation that apigenin blocks the binding of flunitrazepam to GABA_A receptors, displaces flumazenil from the central benzodiazepine binding site, and reduces GABA-activated chloride channels. Apigenin, or 5,7,4'-trihydroxyflavone, is widespread in members of the Asteraceae family and is notably present in *Matricaria chamomilla* L. (*Chamomilla recutita* [L.] Rauschert) or German chamomile (matricaria, *British Pharmaceutical Codex*, 1949).

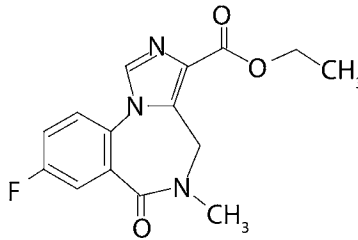


Fig. 52. *Leonotis nepetifolia*.



Apigenin

Flunitrazepam



Flumazenil (Ronmazicon®)

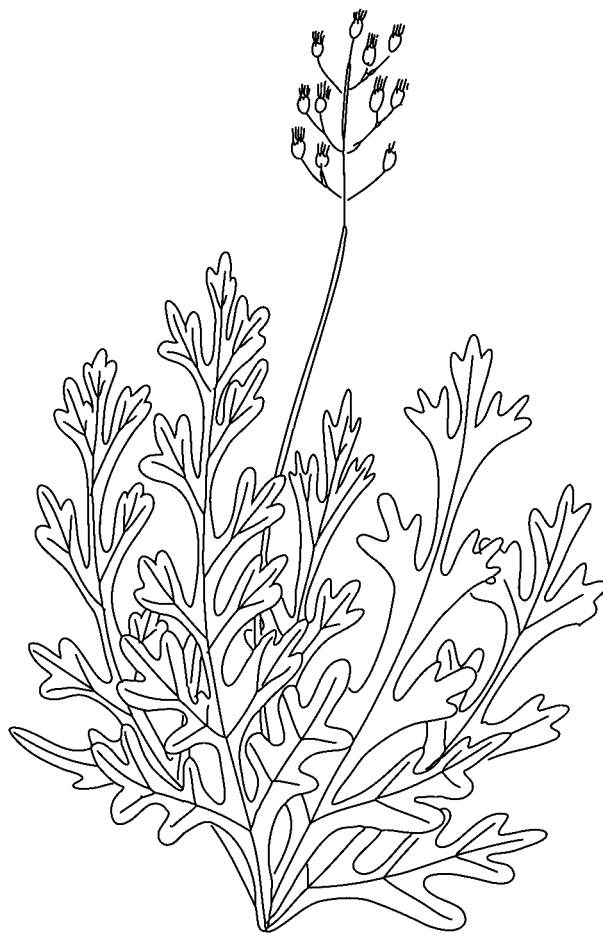
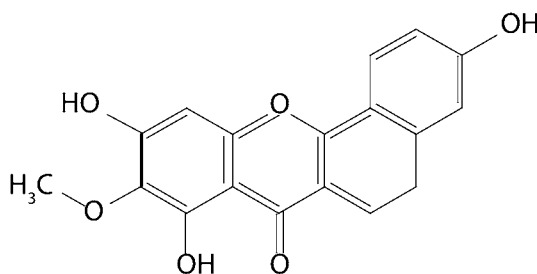


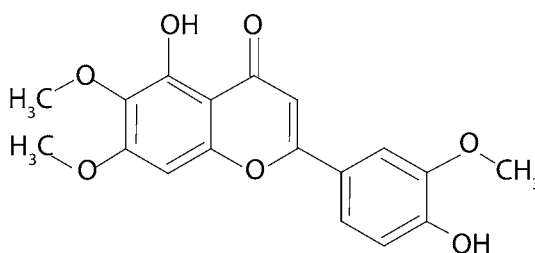
Fig. 53. *Artemisia stelleriana* Bess.

This evidence taken together lends considerable support to the view that sedative Asteraceae owe their activity to the GABAergic property of their flavonoids. One major difficulty seems to be explaining the mechanism by which these polar substances would cross the hemato-encephalic barrier to reach GABA receptors in the brain.

***Artemisia stelleriana* Bess.**, or dusty miller sagewort, beach wormwood; old woman, or *pai hao, fan, lu* (Chinese), is a shrub that grows to 1.20 m in Japan, Korea, China, and Siberia. The whole plant is covered with a glaucous indumentum. The leaves are compound, and the lobes are rounded. The flowers are small, yellowish, and packed in globose capitula (Fig. 53). The medicinal values of *Artemisia stelleriana* Bess. were mentioned by Su Sung (11th century). It has been used internally for food, as carminative, to promote the growth of hair, and to stimulate mental faculties, and externally it provides a remedy for ulcers.



Hispidulin



Cirsilineol

The central nervous properties of the plant have not yet been assessed experimentally. One might set the hypothesis that flavonoids could be involved through interference with the GABAergic nervous system as noticed previously. Some evidence has already been presented that suggests that the *Artemisia* species has an affinity to the GABA_A receptor. Such flavonoids could be hispidulin and cirsilineol isolated from an ethyl acetate extract of *Artemisia herba-alba*, which displaces [³H]-flumazenil radioligand assay, have affinity to the GABA_A receptor. Such flavonoids could be hispidulin and cirsilineol isolated from an ethyl acetate extract of *Artemisia herba-alba* which displace [³H]-flumazenil from GABA(A)-benzodiazepine receptor with IC₅₀ values of 8 μM and 100 μM, respectively (57,58).

Medicinal Orchidaceae

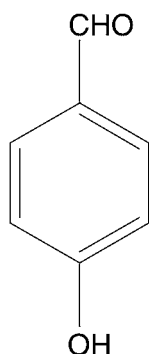
The family Orchidaceae is a large group that, to date, is known to consist of 1000 genera and about 20,000 species of mycotrophic or epiphytic herbs that are recognized by their flowers, which comprise two whorls of three tepals, including a labellum (Fig. 54). Many orchids are cultivated for their spectacular flowers, and *Vanilla planifolia* is the source of a well-known flavoring material. Members of this family are known to elaborate series of isoquinoline derivatives alkaloids, as well as phenylpropanoids and oligostilbenes. About 120 species of Orchidaceae are used for traditional medicine in Asia and the Pacific region and might hold some potential as starting material for the search for GABA receptor antagonists. One of these plants is *Gastrodia elata* Bl.

***Gastrodia elata* Bl.**, or *ch'ih chien, t'ien ma*, is native to East Asia. The plant develops from a rhizome that is about 7 × 2.5 cm. It consists merely in a stem with few flowers at

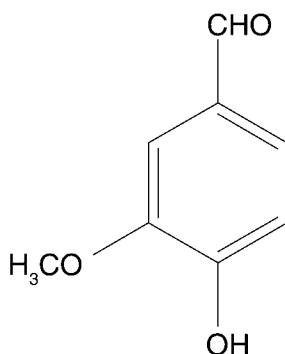


Fig. 54. The botanical hallmark of Orchidaceae: the flowers.

the apex (Fig. 55). In Korea, the plant is used to treat nervous disorders. In China, it had the reputation of being able to “move only in still air,” and the tubers are used to treat headaches, vertigo, paralysis, lumbago, neuralgia, and rheumatism. The drug is believed to stimulate physical, mental and sexual vigor. Ha et al. studied the effects of the constituents of *Gastrodia elata* on the GABAergic neurotransmission and made the interesting observation that 4-hydroxybenzaldehyde and 4-hydroxy-3-methoxybenzaldehyde (vanillin) inhibit the activity of GABA transaminase with IC_{50} values of 4.1 and 5.4 $\mu\text{g/mL}$, respectively, and 4-hydroxy-3-methoxybenzaldehyde dose-dependently increases the binding of [^3H]flunitrazepam to GABA receptors (59,60).



4-hydroxybenzaldehyde.



4-hydroxy-3-methoxybenzaldehyde

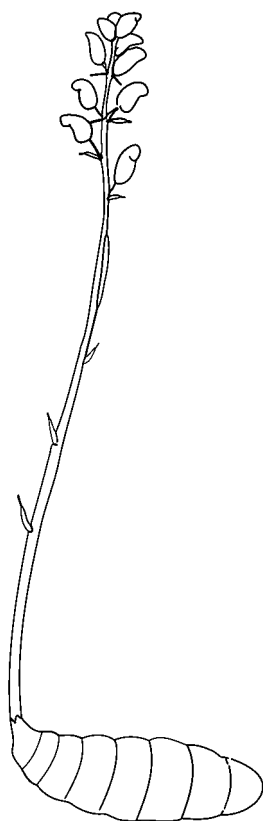


Fig. 55. *Gastrodia elata* Bl.

Acriopsis javanica Reinw. is an epiphyte orchid that grows in Burma, Malaysia, Indonesia, the Philippines, and Papua New Guinea. The pseudobulbs are 5×1.5 cm and develop thick roots. Each pseudobulb produces three leaves, which are linear and $25 \text{ cm} \times 9 \text{ mm}$. The inflorescences are 60 long and branched panicles. The flowers are 7 mm long and pale purple (Fig. 56).

Malays drink a decoction of the whole plant that is used to reduce fever. In Indonesia, the juice expressed from the pseudobulbs is used to assuage earache, and a paste of the pseudobulb is applied externally to lower blood pressure and reduce fever. The pharmacological potential of this plant is unexplored. Is the antipyretic and analgesic property of *Acriopsis javanica* linked to a dopaminergic effect?

Bulbophyllum vaginatum Reich. f. is an epiphytic orchid that grows in Thailand, Indonesia, and Malaysia. The stems are 3 mm in diameter. The petiole is 2×6 mm, swollen, and deeply channeled. The blade is elliptic, thick, spongy, and 8×3 cm. The flowers are arranged in clusters of 12–15 pale yellow, 5-cm-long flowers with elongated corollas (Fig. 57).

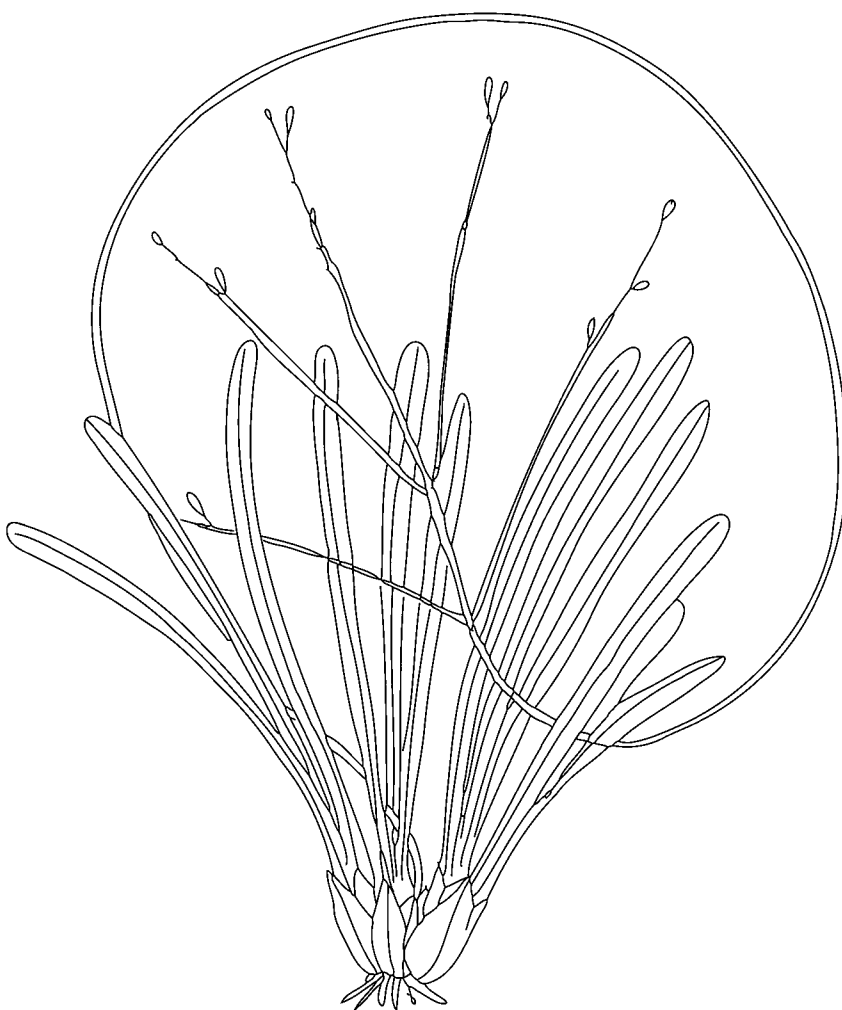
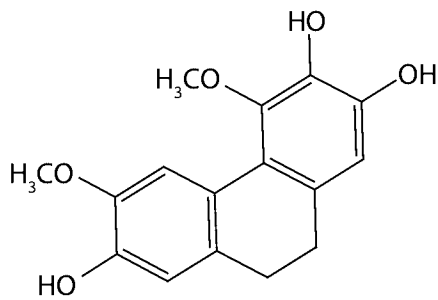


Fig. 56. *Acriopsis javanica*. From Flora of Malaya. Geographical localization: S. Salat on Endau river, Johore. Rocky upper reaches, epiphyte.

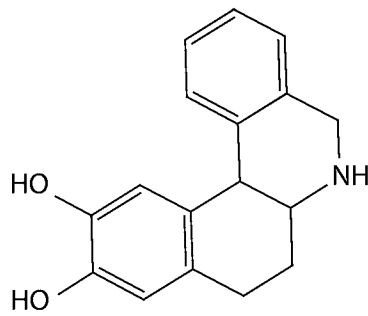
In Malaysia, the juice expressed from the plant is warmed and instilled in the ear to mitigate earache. The pharmacological potential of this orchid is unexplored. Note that an interesting development in *Bulbophyllum* species, and Orchidaceae in general, is the search for dopaminergic phenanthrene. Orchidaceae are well known to elaborate bibenzyls, phenanthrenes, and 9,10-dihydrophenanthrenes. Such compounds are found in *Bulbophyllum vaginatum* Reichb., such as 4,6 dimethoxyphenanthrene-2,3,7-triol and 3,4',5-trihydroxy-3'-methoxybibenzyl (61). An example of a phenanthrenic dopaminergic agent is dihydrexidine, which is a dopamine D₁ receptor agonist (62).



Fig. 57. *Bulbophyllum vaginatum*. From Flora of the Malay Peninsula. Geographical localization: Rantau Panjang, Selangor. 10/30/1930. Field collector: Symington, No: 24330.



4,6 dimethoxyphenanthrene -2,3,7 -triol



Dihydroxidine

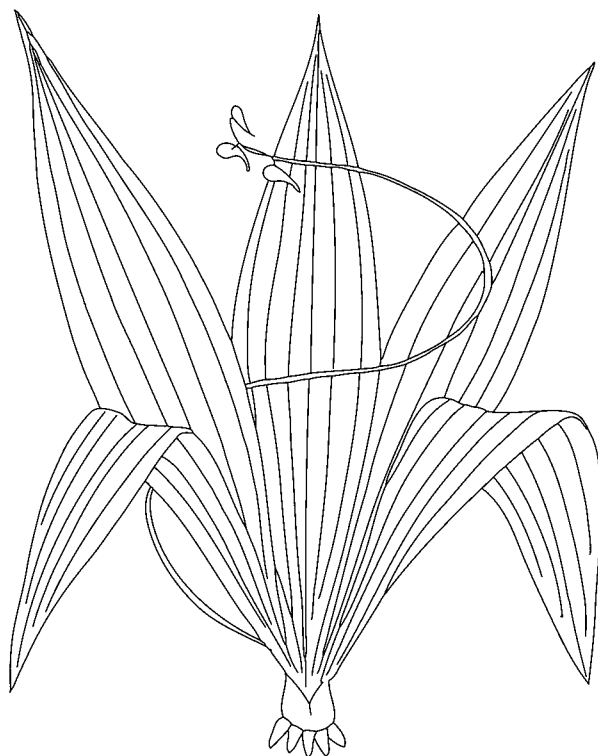


Fig. 58. *Calanthe triplicate*. From Sarawak No 892. Royal Geographical Society, 1977–1978. Mulu Expedition. Field collectors: G. Argent, D Coppins, C. Jermy, 4/5/1978. Geographical localization: Gunong Mulu National Park. 4th Division, Baram District. Hidden Valley (Camp 6). 4° 0.5' North–114° 53' East. In lowland alluvial rainforest under towering limestone.

***Calanthe triplicate* (Villem.) Ames** (*Calanthe veratrifolia* R. Br.), or Christmas orchid, is a large terrestrial orchid that grows in Southeast Asia, Papua New Guinea, and Australia. Each pseudobulb develops three or four large pleated leaves, which are 40 × 9 – 50 × 18 cm. The roots are 1.5 cm long and 2 mm in diameter. The inflorescence is 50 cm long with numerous 1-cm-long white flowers densely packed in a spike. The flowers show white with green rostellum and yellow spots at base of labellum, which is forked (Fig. 58). In Indonesia, the roots are used to treat diarrhea and a paste is applied to swollen parts. A paste of flowers is inserted in the hollow of painful caries. A significant advance in the pharmacology of *Calanthes* species has been provided by the work of Yoshikawa et al. Using bioassay-guided fractionation, they isolated calanthoside, glucoidican, calaliukiuenoside, and calaphenanthrenol from *Calanthe discolor* Lindl. and *Calanthe liukiensis*, which showed an activating effect on skin blood flow and hair restoring activities (63). The dopaminergic and central property of this orchid is unexplored.

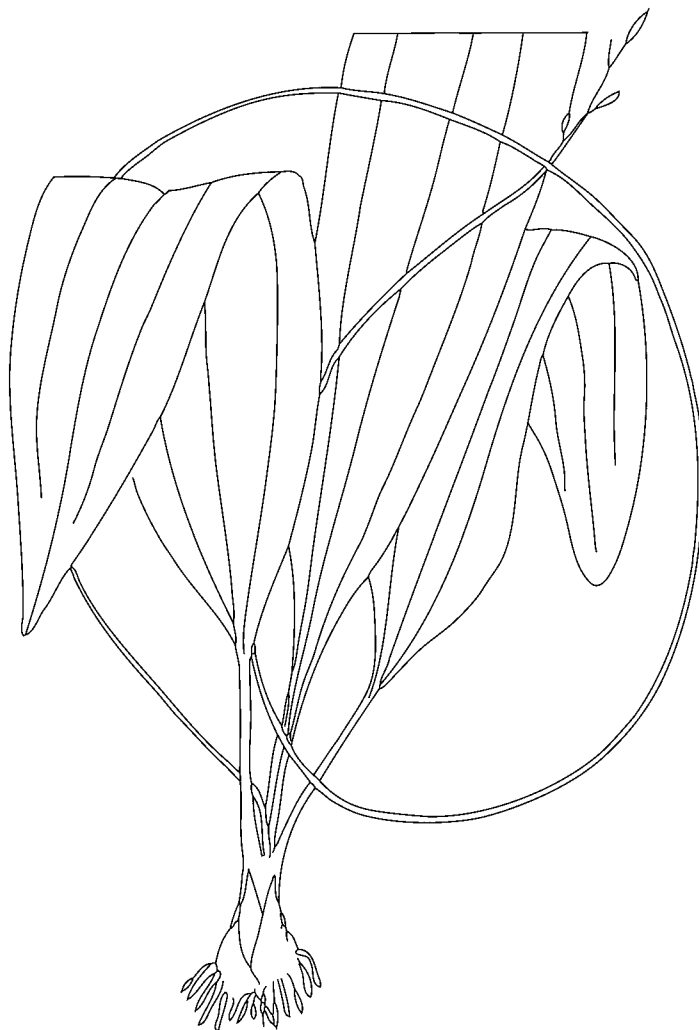


Fig. 59. *Calanthe vestita* Lindl. Flora of Malay Peninsula. Forest Department. Geographical localization: Batu Caves, Selangor. 12/26/1932. Field collector: E.J. Strugnel.

***Calanthe vestita* Lindl.** is a terrestrial orchid that grows in Thailand, Burma, Cambodia, Laos, Vietnam, Malaysia, Sumatra, Java, Borneo, and Celebes. The leaves are 25×5 cm. The petiole is 5 cm long. The inflorescence is 40 cm long. The flowers are white (Fig. 59). In Cambodia, Laos, and Vietnam, a paste of bulbs is applied to painful bones. The pharmacological properties of this plant are currently unknown.

***Dendrobium crumenatum* Sw.**, or pigeon orchid, is an epiphyte orchid that grows in India, China, the Philippines, and Malaysia. The stem is 4 mm in diameter and the bulbs are 2–3 cm around. The leaves are 7×1.3 cm, linear, and fleshy. The petiole is 4×1 mm. The flowers are white (Fig. 60).

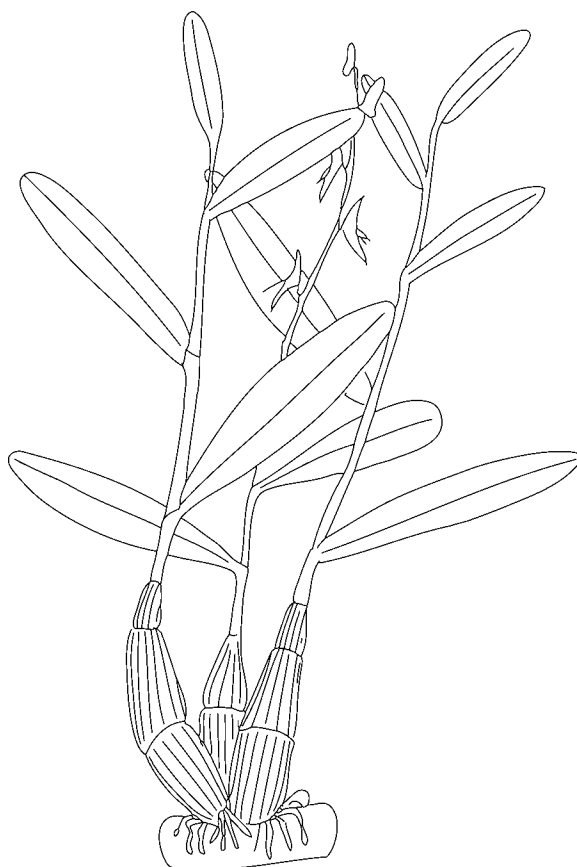
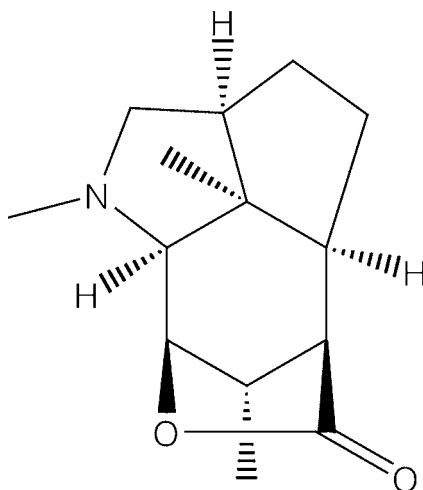


Fig. 60. *Dendrobium crumenatum* L.

The dopaminergic potential of the *Dendrobium* species is, to date, open for exploration. An interesting feature of the *Dendrobium* species is their ability to elaborate sesquiterpene alkaloids, the chemical structure of which resembles the one of strychnine. One such alkaloid is dendrobine, which is widespread in the genus. Kudo et al. noted that dendrobine, isolated from *Dendrobium nobile*, exhibits a strychnine-like presynaptic inhibition in frog spinal cord (64).

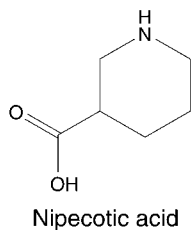
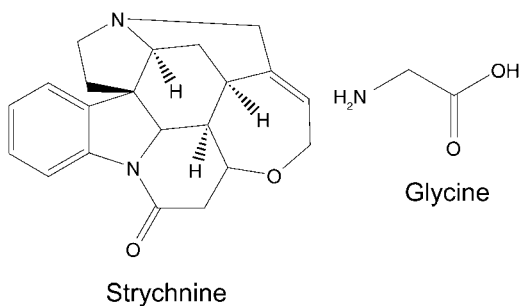
Dendrobine at a dose of 3×10^{-5} M reduced the dorsal root potential and reflex. It provoked a mild hyperpolarization in both dorsal and ventral roots of frog isolated spinal cord. It affected the β -alanine- and taurine-induced depolarization of primary afferent terminals and reversibly blocked the presynaptic inhibition caused by antidromic conditioning stimulation of the ventral root potential induced by repetitive antidromic stimulation of ventral root and lowered maximum. It would be interesting to learn whether further research of the *Dendrobium* species discloses any alkaloid interfering with the glycinergic system, an aspect discussed under the following heading.



Dendrobine

PLANTS INTERFERING WITH THE GLYCINERGIC SYSTEM

Glycine is an important inhibitory neurotransmitter on moto-neurons that operates via the activation of distinct postsynaptic receptors in the hippocampus the spinal cord and brain stem, the pontine reticular formation, and the substantia gelatinosa. Glycine receptors have also been reported within the nucleus tractus solitarius and the nucleus ambiguus, two medullary areas important for central cardiovascular regulation. An interesting development from the glycinergic neurotransmission is to look into the modulation of glycinergic inputs to neurons that control heart rate. A major determinant of glycinergic activity may be opioids, since Gruol and Smith showed that morphine consistently depressed the postsynaptic currents evoked by glycine in cultured fetal mouse spinal cord neurons (65). Decrease in glycine-mediated neurotransmission results in pathologies of muscle tone regulation, which cause motor disturbance, increased muscle tone, and hyperactivity of sensory, visual, and acoustic perception, with higher doses resulting in convulsions and death. Select glycine antagonists have emerged from studies on quinolic acid derivatives, and a current tool for glycinergic binding is nipecotinic acid (66). Perhaps no other single substance has aroused more interest in the field of glycinergic antagonism that strychnine, an indole alkaloid present in the seeds of *Strychnos* species in the family Loganiaceae, and notably the seeds of an Asian plant: *Strychnos nuxvomica* L. (*nux vomica*, *British Pharmacopoeia*, 1963). Strychnine causes tremors and slight twitching of the limbs, followed by sudden convulsions of all muscles. The body becomes arched backward in hyperextension, with the legs and arms extended and the feet turned inward in a position called "episthotonos." The facial muscles produce a characteristic grinning expression known as *risus sardonius*. Death from medullary paralysis usually follows the second or fifth seizure.

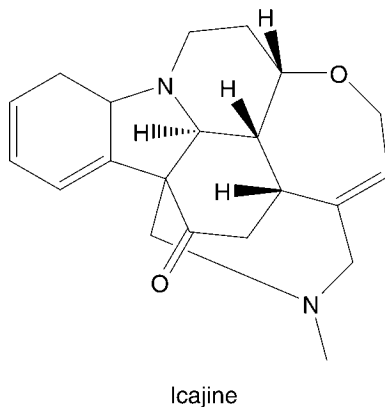


Although there have been many studies on strychnine itself, the evidence available shows that much less work has been done with the search for glycinergic agents from flowering plants, and we can reasonably expect the discovery of major glycinergic agents in the coming decade. An interesting source for such agents is the medicinal flora of Asia and Pacific, which encompasses several *Strychnos* species.

Medicinal Loganiaceae

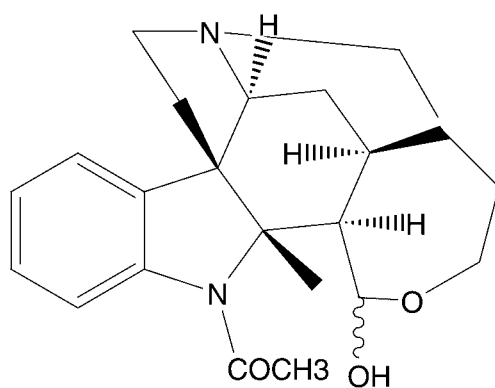


The family Loganiaceae consists of about 20 genera and 500 species of tropical trees, shrubs, or climbers commonly producing iridoids and monoterpenoid indole alkaloids formed by the condensation of tryptamine and secologanin (an iridoid). Examples of pharmaceutical products of loganiaceous origin are the dried ripe seeds of *S. nuxvomica* L. (*nux vomica*, *British Pharmacopoeia*, 1963) and *Strychnos ignatii* (*ignatia*, *British Pharmaceutical Codex*, 1934), which have been used as bitter tonic remedies and as ingredients of purgative pills and tablets on account of monoterpenoid indole alkaloids, such as strychnine (*British Pharmaceutical Codex*, 1959), which blocks the glycinergic receptors.



Strychnine was elucidated in 1947 owing to the major contribution of H. Leuchs and Sir Robert Robinson. Since then, strychnine has been characterized from several *Strychnos* species: *Strychnos ignatii* Berg., *Strychnos wallichiana* Steud. Ex DC, and *Strychnos lucida* R. Br. The strong convulsive strychnine is accompanied by series of related alkaloids, such as brucine, colubrine, vomacine, and novacine. Strychnine and related alkaloids could be present in other species, but the complete chemical composition of many *Strychnos* species is as yet unknown (66). In the Pacific Rim, about 20 species of Loganiaceae, including *Strychnos ignatii* Berg., *Strychnos gauthierana* Pierre ex Dop, *Strychnos lucida* R. Br., *Strychnos minor* Dennst., and *Strychnos axillaris* Colebr., are medicinal and often used to invigorate, counteract putrefaction, treat eye diseases, and expel worms from intestines.

***Strychnos ignatii* Berg.** (*Strychnos beccarii* Gilg, *Strychnos cuspidata* A.W. Hills, *Strychnos ovalifolia* Wall, *Strychnos pseudotieute* A.W. Hill, *Strychnos tieute* Lesch. *Ignatia amara* L. f.; *Ignatiana philippinica* Lour., *Strychnos hainanensis* Merr. & Chun, *Strychnos ovalifolia* Wall. ex G. Don.), or *lu sung kuo* (Chinese), *umpas naga*, or *akar ipoh* (Malay), is a climber that grows in open woodlands, on limestone, scrub, or sometimes along river banks up to 800 m in China, Indonesia, Malaysia, the Philippines, Thailand, and Vietnam. The plant grows to a length of 20 m. The stems are grayish-brown, lenticelled, with tendrils. The leaves are simple and opposite; the flowers are yellowish, salver-shaped, 1.7 cm long, and papillose. The fruits are cream-green to orange berries up to 10 cm in diameter, containing several seeds that are ovate and flat (Fig. 61). The dried ripened seeds, or St. Ignatius beans (*ignatia*, *British Pharmaceutical Codex*, 1934), containing 2.5 to 3% of brucine and strychnine have been used as bitter and tonic in the form of tinctures, cachets, and piles, and the plant is still used in homeotherapy. In China, the seeds were mentioned in the Pentsao for their bitterness and toxicity. The drug is highly valued by the Chinese physicians who call it “precious bean” and who used it as counter-poison in ague, to expel intestinal worms, and treat postpartum difficulties. In Cambodia, Laos, and Vietnam, the seeds are used to invigorate and expel worms from the intestine. In the Philippines, the bark is used to reduce fever and assuage stomach pains. The seeds contain strychnine, brucine, pseudostrychnine, and pseudobrucine (68).



Diaboline

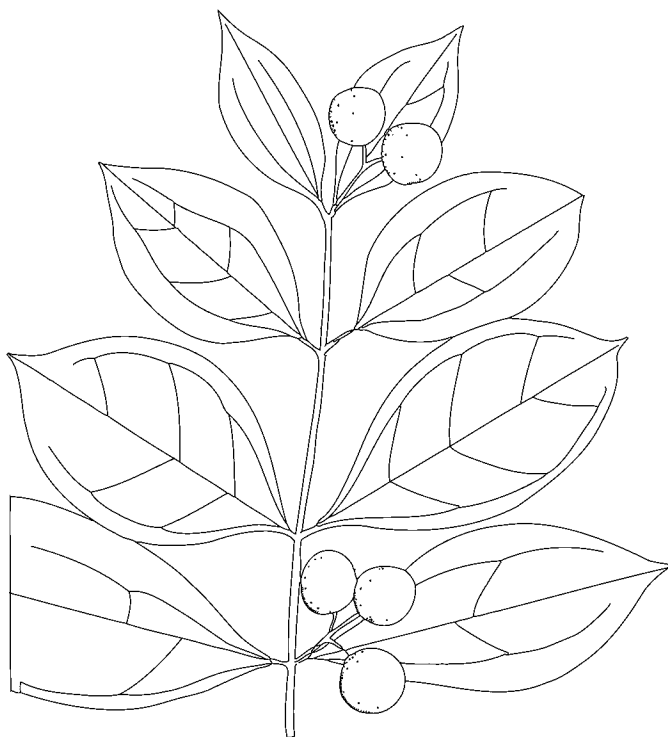


Fig. 61. *Strychnos ignatii* Berg. From Flora of Malaya. Kep: FRI No 15383. 7/21/1970. Field collector: T.C. Whitmore. Geographical localization: National Park, Pahang, Ulu Tembeling. Ridge northwest of Tg Bunhkal in low dense forest.

***Strychnos minor* Dennst.** (*Strychnos multiflora* Benth.) is a climber that grows to a height of 15 m in the rainforests of India, Thailand, Malaysia, Indonesia, and the Philippines. The stems are terete, subglabrous, and develop pairs of hooks at nodes. The leaves are opposite, papery, conspicuously triple-nerved to 10 cm in length. The fruits are berries that are bluish at first and 1.4 cm in diameter (Fig. 62). It is used in the Philippines to treat throat trouble. A decoction of bark is used as an emmenagogue, and the Negritos chew the bark to treat prolapse of the uterus. The seeds are poisonous on probable account of strychnine and congeners.

***Strychnos axillaris* Colebr.** (*Strychnos pubescens* C.B. Clarck), or *ye hua ma qian* (Chinese), *chewong*, or *tenchong gendeng* (Malay), is a climber that grows to 20 m long in mountain forests, forest edges, and to 800 m altitude in a geographical area spanning China, Cambodia, India, Indonesia, Laos, Malaysia, Thailand, Vietnam, and Australia. Stems, petioles, and blades are velvety. The stem shows axillary hooks that are spirally curved. Leaf blades are elliptic, narrowly elliptic, ovate, or suborbicular. The berries are ovoid to globose, and up to 2 cm in diameter and contain one or two seeds (Fig. 63). The seeds have been used to make arrow poison. The chemical composition of the seeds is currently unknown.

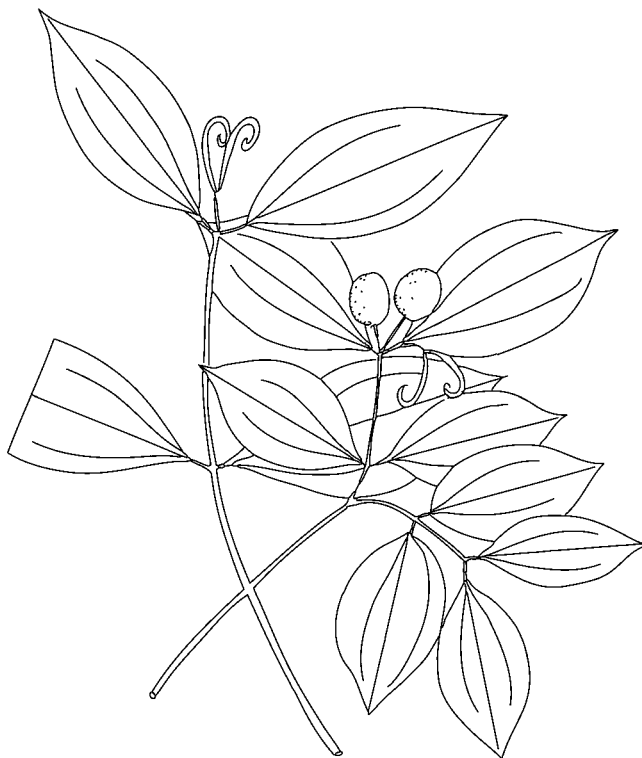
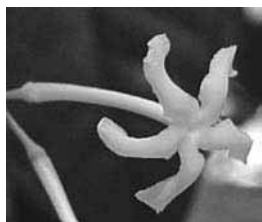


Fig. 62. *Strychnos minor* Dennst. From Plants of South India, C.E. Ridsdale 395. date: 7/12/1976. Geographical localization: Walaiyar Estate, Papanasam, Tamil Nadu. In ever-green forest. Distributed by the Rijkskherbarium, Leiden.

Medicinal Apocynaceae



A group of plants of interest when searching for glycine receptor antagonists are the Apocynaceae, the indole alkaloids of which appear to have glycinergic activities. Pathama et al. made the interesting observation that corymine, an indole alkaloid extracted from the leaves of a medicinal plant of Malaysia and Thailand, *Hunteria zeylanica* (Retz.) Gardn. & Thw. (*Hunteria corymbosa* Roxb, *Hunteria roxburghiana* sensu Ridl.), potentiates the convulsions induced by either strychnine or picrotoxin at doses of 2, 8, and 15 mg/kg in mice and inhibits glycine-induced chloride current in *Xenopus* oocytes non-competitively by interacting with a site different from that of 4,4'-diisothiocyanostilbene-2,2'-disulfonic acid, a Cl⁻ channel blocker (69). All this evidence taken together lends considerable support to the view that monoterpenoid alkaloid-producing families of flowering plants such as Apocynaceae, Loganiaceae, and Rubiaceae represent an exciting reservoir of potential glycinergic agents.

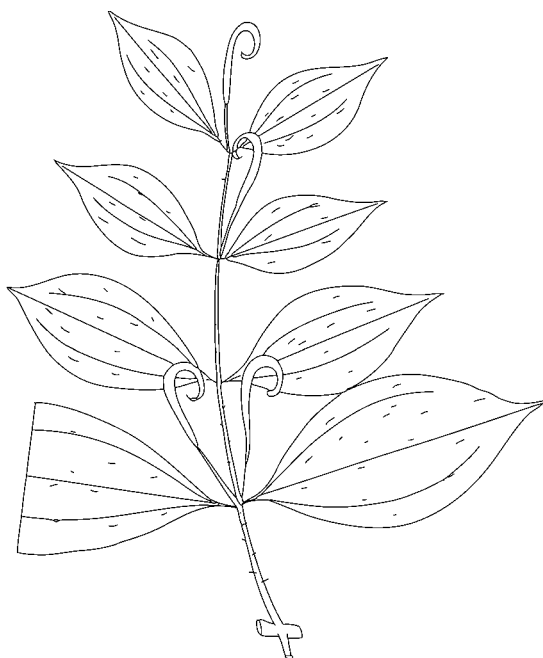
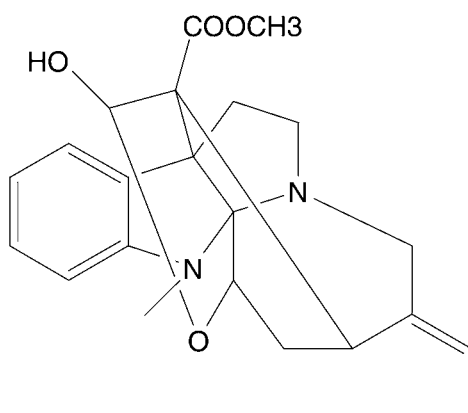


Fig. 63. *Strychnos axillaris* Colebr. Department of Wildlife and National Parks. Plants of Krau Wildlife Reserve, Malaysia. Field collectors: Hanne Christensen and Rozidan M. Geographical localization: 3° 36' North–102° 8' East. In mature forest on level ground.



Corymine

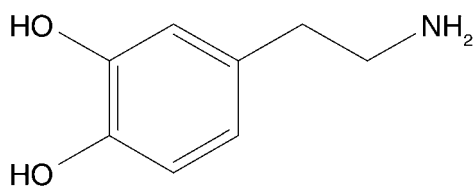
PLANTS AFFECTING THE DOPAMINERGIC NEUROTRANSMISSION

Dopamine is a catecholamine neurotransmitter in the CNS and at some ganglia in the autonomic nervous system. To date, three main types of receptors have been found: D₁, D₂, and D₃. The main dopaminergic systems in the brain are the nigro-neostriatal



Fig. 64. *Hunteria zeylanica* (Retz.) Gardn. & Thw. From KLU 1658. Field collector: 4/17/1970, E. Soepadmo. Geographical localization: Sempam River, Raub, Pahang, altitude: 2000 feet, Malaysia. Botanical identification: Margraf, 1973.

system, which is concerned with the control of locomotor activity; the midbrain mesolimbic forebrain system, which is involved with behavior; and the tubero-infundibular system of the hypothalamus, which releases dopamine into the portal vessels and thereby inhibits pituitary prolactin disease (Fig. 65).



Dopamine

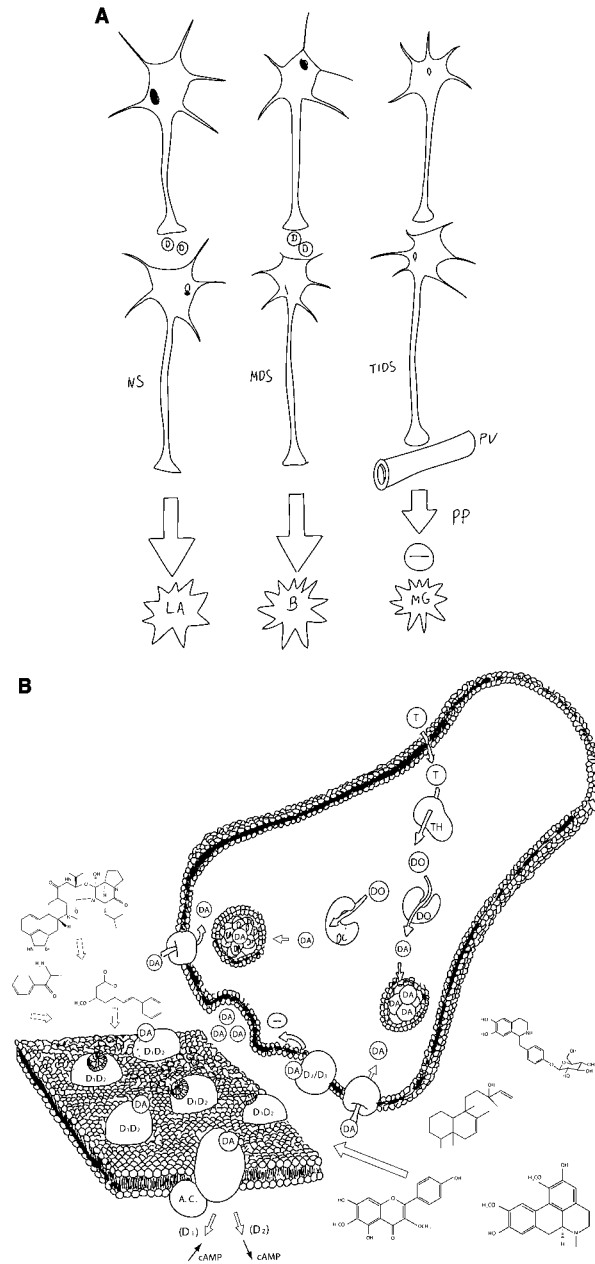
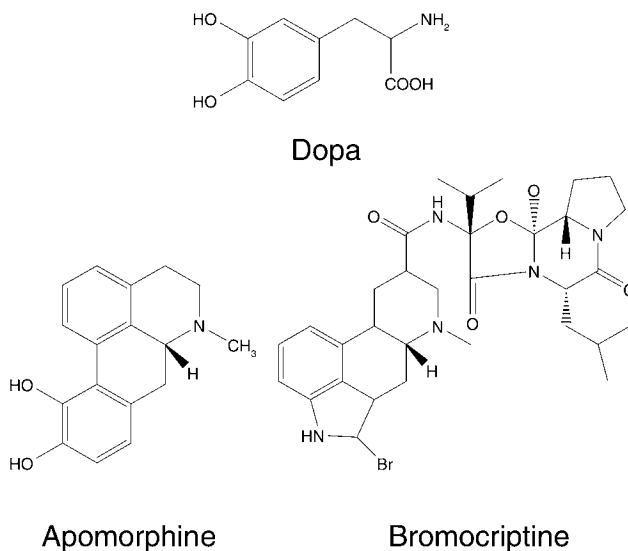


Fig. 65. **(A)** Dopaminergic system: the three important brain dopaminergic systems. **(B)** Dopaminergic system: the dopaminergic neurons. NS, nigrostriatal dopaminergic neurone; PP, prolactin pituitary, PV, portal vein; MG, mammary gland; MDS, mesolimbic dopaminergic system; B, behaviour; LA, locomotor activity; TIDS, tuboinfundibular dopaminergic system; DA, dopamine; DO, DOPA; DC, DOPA decarboxylase; T, tyramine; TH, tyrosine hydroxylase; D1/D2, dopaminergic receptor D₁ or D₂; D2/D3, dopaminergic receptor D₂ or D₃; AC, adenylylate cyclase.

In normal physiological conditions, the dopaminergic neurons of the substantia nigra control the cholinergic output but if they do not, as is the case in Parkinsonism, the skeletal muscles experience tremors, rigidity, and akynesia. L-DOPA given by mouth is effective in restoring the ability to initiate movements and is the most effective treatment for this condition; however, high doses are needed that produce nausea, vomiting, and hypotension. Because of the side effects associated with L-DOPA treatment, a number of dopamine receptor agonists have been tried including apomorphine, and ergolines such as bromocriptine. Another alternative to treat Parkinsonism is the use of anticholinergic agents, such as crude extract of *Atropa belladonna* L. (Solanaceae) and, more recently, anticholinergic alkaloids and their derivatives, which attenuate the tremor and relieve the muscular rigidity but are better to be used sparingly in elderly, as these these induce heavy nervous side effects. In summary, the drugs developed for the last 30 years have led to a significant reduction in the mortality of patients with Parkinsonism, but fail to prevent the progression of the disease.



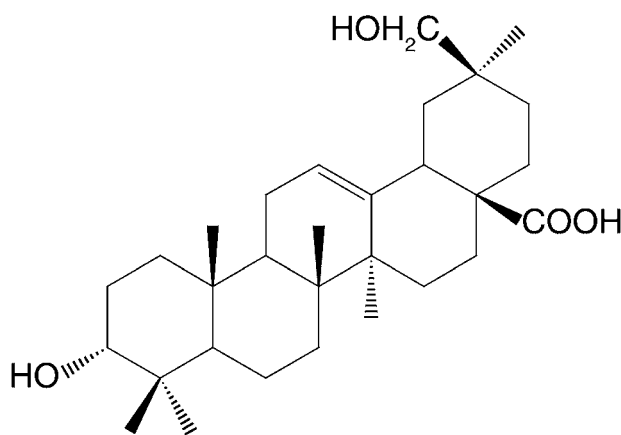
An interesting development from dopaminergic agents is the search for drugs for the treatment of premenstrual syndrome because pituitary prolactin release is under tonic hypothalamic inhibition by dopamine. Besides, the dopaminergic system plays an important role in the pathophysiology of migraine, and a dopamine antagonist such as prochlorperazine has exhibited antimigraine properties in animals by possible central amplification of cholinergic transmission. There is therefore a need for original dopaminergic agents, and one of the possible more exciting sources for such agents is the medicinal flora of Asia and the Pacific. The evidence available so far suggests that such agents would be present in the following medicinal plants.

Medicinal Araliaceae

The traditional systems of medicine of Asia and the Pacific use about 50 species of plant species classified within the family Araliaceae that are of medicinal value and notably used as tonic. Examples of such plants are of *Panax ginseng* C. A. Meyer (ginseng), *Panax notoginseng* Burk. (*san chi ginseng*), *Panax japonicus* C. A. Meyer (Japanese ginseng), and *Acanthopanax senticosus* (Siberian ginseng). The evidence for the existence of immunostimulating and anabolic saponins in *Panax* and *Acanthopanax* species is strong and well documented, but much less work has been done with the dopaminergic potentials of these saponins.

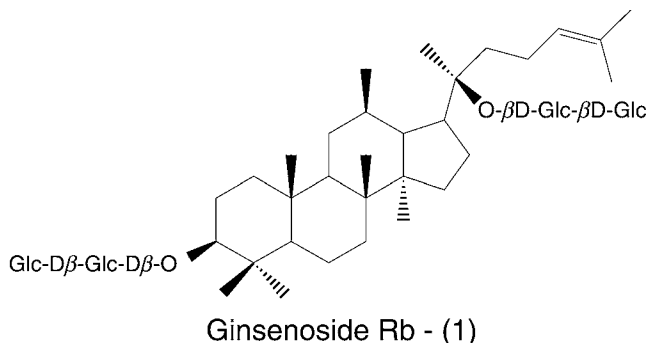
***Acanthopanax gracilistylus* W. W. Sm.** (*Acanthopanax spinosus* Miq, *Eleutherococcus gracilistylus*), or *wu chia* (Chinese), *gokahi* (Japanese), or *ogap'i* (Korean), is a deciduous shrub growing to 3 m wild in East Asia and China. The leaves are palmatilobed and show five folioles that are elliptic lanceolate, fleshy, and serrate. The inflorescence consists of small umbels up to 6 cm long. The drug consists of the root bark found in Chinese pharmacies in the form of yellowish-brown pieces; it is used for rheumatism, general debility, impotency, and muscular pains. In Malaysia, the plant is used as carminative.

Fujikawa et al. made the interesting observation that an extract from the stem bark given orally at a dose of 250 mg/kg once a day for 2 weeks protects rats against MPTP-induced Parkinsonian bradykinesia and catalepsy and inhibited neuronal loss of dopamine (70). The active constituents involved here are unknown. Note that the plant abounds with pentacyclic oleanene saponins (71–73). Note that *Acanthopanax* species are known to elaborate a series of diterpenes, a group that has the potency to bind to dopamine receptors, as reported in *Vitex agnus-castus*. Are diterpenes involved in the dopaminergic properties of *Acanthopanax gracilistylus* W. W. Sm.?



Oleanene aglycone

There is an expanding body of evidence to suggest that ginsenosides have a protective effect on the dopaminergic system. Radad et al. made a careful study on the effects of ginsenosides Rb1 and Rg1 on dopaminergic neurones from embryonic mouse mesencephalon and showed that these saponins protect neurons against the degenerative effects of 1-methyl-4-phenylpyridinium-iodide (74). In addition, pretreatment with ginseng total saponin prevents the methamphetamine-induced striatal dopaminergic depletions (75).



***Acanthopanax trifoliatum* (L.) Merr.** (*Acanthopanax aculeatum* Seem, *Eleutherococcus trifoliatum*) is a deciduous shrub that grows up to 6 m in a geographical area ranging from the eastern Himalayas to Japan and south into Cambodia, Laos, Vietnam, and the Philippines. The stems are light brown and smooth. The leaves are spiral and trifoliate; the folioles are broadly elliptic, grayish-green, and glossy. The folioles are 5 × 3 cm and show four pairs of secondary nerves. The apex is acuminate, the base is rounded, and the margin is crenate at the apex. The inflorescences are globose umbels, which are 3 cm in diameter and bear about eight flowers (Fig. 66).

The plant is used to treat leprosy; the roots are used to heal ulcers and to cure ringworm infection. A decoction of the leaves is drunk to treat tuberculosis and to improve general weakness. In Cambodia, Laos, and Vietnam, an infusion of the bark is used to correct nervous affections. The plant is known to elaborate lupane triterpene saponins and kaurane diterpenes including 16- α H, 17-isovalerate-ent-kauran-19-oic acid, which strongly inhibited the enzymatic activity of cyclooxygenase in vitro (76,77).

***Acanthopanax ricinifolius* Seem.** (*Kalopanax ricinifolius* [Sieb. & Zucc.] Miq, *Kalopanax pictus* [Thunb.] Nakai, *Acer pictum* [Thunb], *Acanthopanax ricinifolium* [Sieb. & Zucc.] Seem, *Kalopanax septemlobus* Koidz. var *septemlobus*, *Panax ricinifolium* Siebold & Zucc, *Kalopanax ricinifolium* Miq, *Kalopanax pictum* Nakai), or prickly ginseng, castor *Aralia*, prickly castor oil tree, or *tzu ch'iu-shu* (Chinese), is a deciduous tree that grows to 25 m in Siberia, Korea, Japan, and China. The bark is gray mottled with yellowish-white; the stems are thorny and the leaves simple and palmate (Fig. 67).

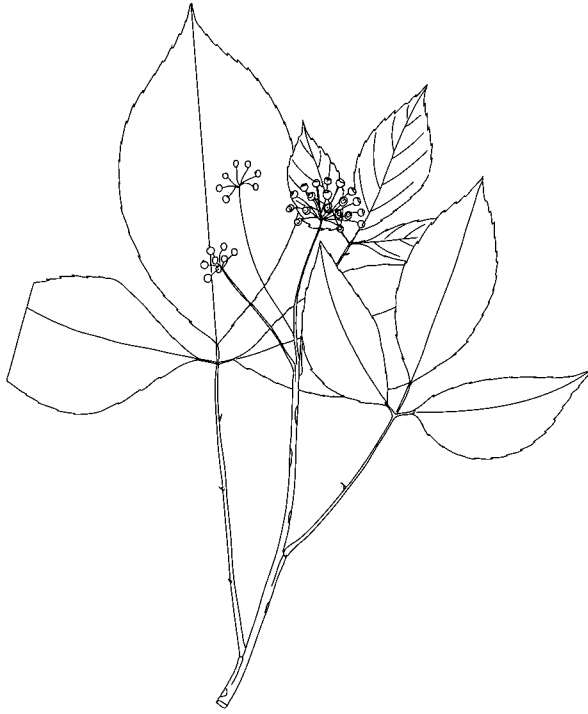
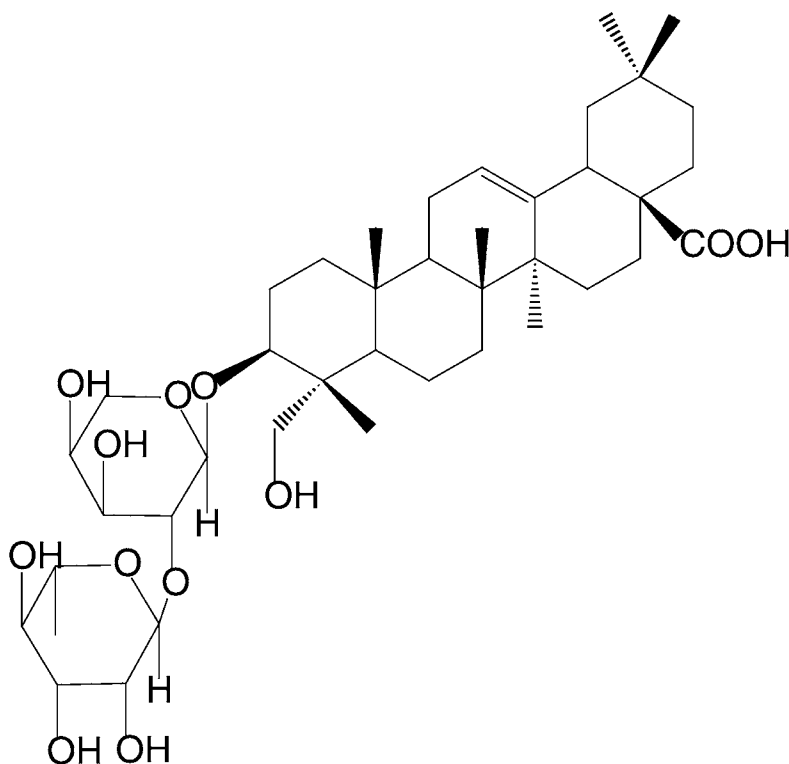


Fig. 66. *Acanthopanax trifoliatum* (L.) Merr.



Fig. 67. *Acanthopanax ricinifolius* Seem.



Kalopanaxsaponin A

The wood is valuable as timber. In China, the bark and leaves are used for insecticide, for the treatment of skin diseases, and to heal sores and ulcers. In Korea, the bark is used for the treatment of rheumatism, cold, and cough. In Cambodia, Laos, and Vietnam, an infusion of leaves is drunk to promote digestion. The anti-inflammatory property of the plant is confirmed *in vitro* and thought to be imparted by saponins, including kalopanaxsaponin A and pictoside A, which elicited significant anti-inflammatory and anti-oxidant activity in rodents (78–82). What is the dopaminergic activity of kalopanaxsaponin A and pictoside A?

Medicinal Verbenaceae

An interesting feature of the genus *Vitex* is used in several traditional systems of medicine as birth control and to treat gynecological disorders. Most of these plants contain ecdysteroids, the hormonal and especially gynecological effect of which remains to be clarified. Clinical trials showed that the fruits of *Vitex agnus-castus* (chaste tree) are effective in the treatment of the premenstrual syndrome (83). The question that might arise is to know whether the *Vitex* species owes these premenstrual and gynecological properties to a mechanism involving the dopaminergic system. At present, it is not possible to answer this question but some clinical evidence has already

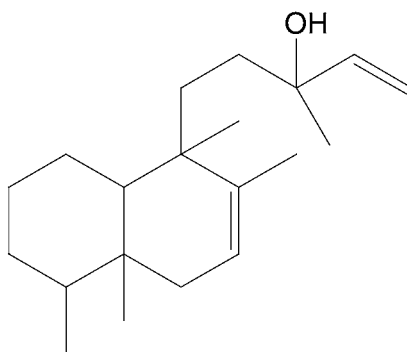


Fig. 68. *Vitex negundo* L.

been presented indicating that premenstrual mastodynia (mastalgia) is improved by intake of *V. agnus-castus* via inhibition of prolactine secretion. Further research in this topic is obviously needed.

***Vitex negundo* L.** (*Vitex spicata* Lour., *Vitex paniculata* Lamk., *Vitex incisa* Lam.), or Indian privet, five-leaved chaste tree *kiyubantin* (Burmese), *mu ching* (Chinese), *agnocasto* (Philippino), *nochi* (Tamil), or *swaha* (Sanskrit), is a treelet of the Asia-Pacific region. The stems are quadrangular and velvety. The leaves are decussate, exstipulate, three- to five-foliolate, and glaucous below, and show 9–13 pairs of secondary nerves. The inflorescences are terminal, with panicles of about 20 cm long of several bluish-purple flowers. The fruits are black berries (Fig. 68). In China, the flowers are used to

treat rheumatic difficulties, colds, cough, angina, and gonorrhoea. The leaves are used to calm itchiness of eczematous eruptions. The roots are used to treat colds and rheumatisms, and the stems are used to soothe burns and scalds. An infusion of the stems is drunk to treat headache, dizziness, convulsions of children, cough, mental unrest, and to promote wakefulness. In the Philippines, *Vitex negundo* L. is used to promote milk secretion and menses. In India, the plant is used to soothe inflammation and to calm itching. The anti-inflammatory property of *Vitex negundo* L. is confirmed: a water extract of the leaves protects rats against carrageenan-induced rat paw edema, formaldehyde-induced rat paw edema, and hot-plate test. Although there have been many studies on the anti-inflammatory properties of the plant, much less work has been done on the psychopharmacological and especially dopaminergic properties of this plant (84,85). Note that the fruits of *Vitex agnus-castus* contain dopaminergic diterpenes known as clerodadienols, which exhibit prolactin-suppressive effects (86). What are the diterpenic contents of *Vitex negundo*?

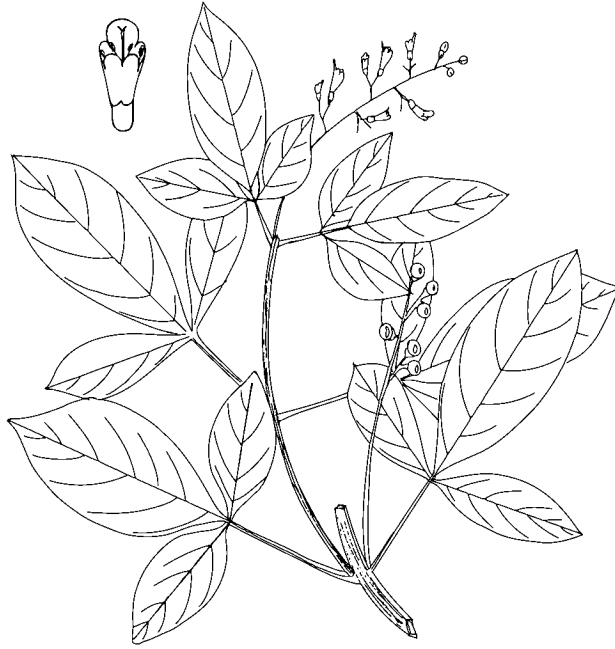
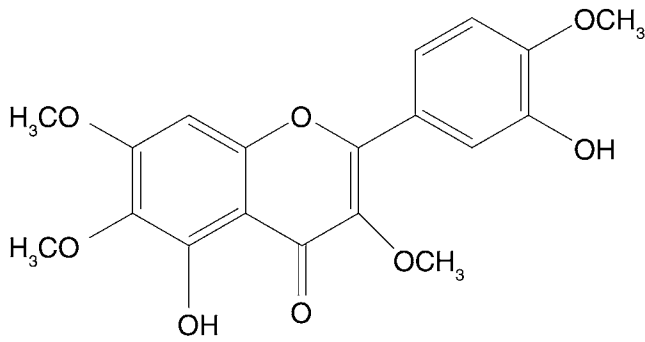


Clerodadienol

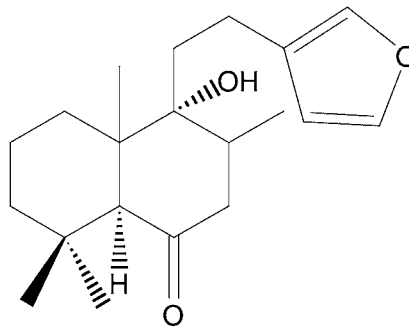
***Vitex trifolia* L.** (*Vitex rotundifolia* L.f., *Vitex lagundi* Ridl. *Vitex repens* Blanco), or hand of Mary, *man jing* (Chinese), *dangla* (Philippino), *galumi* (Indonesian), *lenggundi* (Malay), *pitipitikoto* (Papua New Guinea), *khon thiso* (Thai), or *majn kinh* (Vietnamese), is a treelet that grows to a height of 5 m tall in Taiwan, China, Southeast Asia, Australia, and the Pacific Islands. The leaves are three-foliolate, with each foliole lanceolate or obovate, and showing eight pairs of secondary nerves. The flowers are purplish to bluish-purple, and 6 mm to 10 cm long. The fruits are black, subglobose, and with 5-mm-diameter drupes (Fig. 69).

The drug consists of the dried berries that are prescribed for headache, catarrh, watery eyes, and are used to promote beard growth. In Cambodia, Laos, and Vietnam, the berries are used to treat conjunctivitis, dropsy, toothache, and as a remedy for swollen breast. In Malaysia, the leaves are used to assuage headache externally, and internally are used to treat tuberculosis and fever.

The plant is attracting a great deal of interest on account of its ability to elaborate labdane diterpenes vitexilactone, 6-acetoxy-9-hydroxy-13(14)-labden-16,15-olide, rotundifuran,

Fig. 69. *Vitex trifolia* L.

Vitexicarpin



Rotundifuran



Fig. 70. *Vitex quinata* (Lour.) F.N. Will.

vitetrifolin, and vitetrifolin E, and a flavonoid viteicarpin, which induces apoptosis of both tsFT210 and K562 cell-lines (87,88). Note that the concomitance of use for headache and breast troubles might be indicative of a possible dopaminergic property; however, this remains to be confirmed or infirmed experimentally. Are dopaminergic labdanes involved here or are flavonoids, such as vitexicarpin? Naidu et al. made the exiting suggestion that the analgesic activity of flavonoids, such as quercetin, could be mediated by D_2 -dopamine receptors (89). Are flavonoids, especially the liposoluble ones, holding potentials for the treatment of Parkinsonism?

***Vitex quinata* (Lour.) F.N. Will.** (*Vitex heterophylla* Roxb.), or *shan mu jing* (Chinese), is a tree that grows to a height of 12 m in Taiwan, China, India, Indonesia, Japan, Malaysia, the Philippines, and Thailand. The young stems are pubescent and quadrangular. The leaves are decussate and three- to five-foliolate, thinly coriaceous, glossy, and 5–20 cm \times 2.5–8.5 cm (Fig. 70). The inflorescences are terminal lax, densely yellowish-brown, pubescent panicles of yellowish, bilabiate flowers. The fruits are black drupes. In Taiwan, Cambodia, Laos, and Vietnam, the fruits are used to treat neuralgia and the leaves are used as tea. The bark is used to invigorate and to stimulate appetite. To date, the pharmacological potential of *Vitex quinata* (Lour.) F.N. Will. is unexplored. It would be interesting whether further study results in the characterization of dopaminergic agents from this plant.

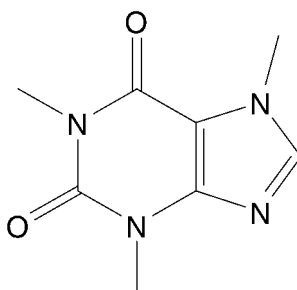
***Vitex vestita* Wallich ex Schauer**, or *huang mao mu jing* (Chinese), is a tree that grows to a height of 8 m tall in China and Southeast Asia. The stems are densely yellow-brown and pubescent. Leaves are three-foliolate; the folioles are elliptic-oblong to elliptic,

membranous, and 2.5–15 cm × 1.5–8 cm. The inflorescence is dichotomous cymes of small yellowish bilabiate flowers. The fruits are black drupes of up to 8 mm long. In Malaysia and Indonesia, the plant is used to cause abortion. The dopaminergic potential of the plant is unknown. Note that some evidence has already been presented indicating that prolactin disorders might be responsible for habitual abortion. Ando et al. showed that patients with a history of recurrent spontaneous abortion and prolactin disorders without impaired corpus luteum function treated with bromocriptine were able to maintain pregnancy (90). An interesting development from *Vitex vestita* and other plants traditionally used for inducing abortion would be to assess any dopaminergic activities and to characterize the active principles responsible for such activity.

Medicinal Sapindaceae

The family Sapindaceae consists of 140 genera and 1500 species of trees widespread in tropical and subtropical regions. Classic examples of Sapindaceae are the fruit trees *Nephelium lappaceum* L. and *Litchi chinensis* Sonn., which provide rambutan and litchi, respectively. Chemically Sapindaceae are well known to abound with saponins and tannins. An example of ornamental Sapindaceae is *Koelreuteria paniculata* L., or golden rain tree, cultivated in temperate regions. The berries of *Sapindus saponaria* L., were used as soap by South American Indians, hence the origin of the word *Sapindus* from *sapo* and *Indus* or the soap of the Indies.

It can be said that the present state of knowledge on the pharmacological potential of this large family is virtually vestigial. A classic example of Sapindaceae of neuropharmacological interest is *Paullinia cupana*, used by the Tapajoz Indians of the Amazon region to make a tonic beverage since very early times. The dried paste prepared from the roasted seeds containing not less than 45% of caffeine has been used for the treatment of headache and astringent in diarrhea (*British Pharmaceutical Codex*, 1934, *Brazilian Pharmacopoeia*, 1959). Today a large number of phytopharmaceutical products containing guarana are on the market. Another example is *Paullinia yopo*, used for the same purpose by Colombian Indians. Caffeine is the most widely consumed psychostimulant substance, being self-administered throughout a wide range of conditions and present in numerous dietary products including coffee, tea, cola drinks, chocolate, candy, and cocoa.



Caffeine

The main mechanism of action of caffeine occurs via the blockade of adenosine receptors in the CNS. Adenosine is an autacoid, which is involved in the modulation of behavior, oxygenation of cells, and dilatation of cerebral and coronary blood vessels and indirectly inhibits the release of dopamine. The blockade of adenosine receptors by caffeine increases the activity of dopamine, which is implicated in the effects of caffeine (91). The question that arises from this observation is to know whether or not adenosine antagonists hold potential for the treatment of Parkinsonism, and further study on the adenosine receptor antagonists from medicinal plants should be encouraged. A possible source for such agents could be the medicinal flora of Asia and the Pacific, among which is the family Sapindaceae.

***Erioglossum rubiginosum* (Roxb.) Bl.** (*Erioglossum edule* Bl, *Sapindus rubiginosus* Roxb, *Lepisanthes rubiginosa* (Roxb.) Leenh. is a treelet that grows up to 10 m tall and is common in coastal forests throughout tropical Asia. The stems are hairy; the leaves are paripinnate without stipules with a woolly rachis. Four to six pairs of folioles, 10–12.5 cm × 3.5–4.5 cm. The inflorescences are terminal panicles of small flowers with four petals and eight stamens. The fruits are blackish, edible, and fleshy. In Malaysia, a decoction of roots is used to mitigate fever and the leaves are used externally to treat skin disease. In Indonesia, the young stems are eaten to induce sleeping. An aqueous extract of pericarp of the fruits at intraperitoneal doses of 20 and 100 mg/kg significantly reduced the spontaneous locomotor activity, and at 100 mg/kg, increased the thiopental-induced sleeping time and affinity toward dopaminergic receptors, inhibited the apomorphine-induced climbing behavior in mice, and exhibited affinity toward D₂ receptors, suggesting dopamine D₂ antagonism (95).

***Sapindus mukorossi* Gaertn.**, or soapnut, Indian filbert, china berry, *arishta*, *ritha* (Sanskrit), *wu huan tzu*, *mu huan tzu*, *fei chi tzu*, *p'u ti tzu*, or *kuei chien ch'ou* (Chinese), is a large tree. The leaves are pinnate, grow up to 50 cm long, and show four to six pairs of folioles. The flowers are small, yellowish 3–4 mm long on terminal panicles. The fruits are globose, 2 cm across, and yellowish (Fig. 71). The drug consists of the dried seeds. In China, the seeds are roasted and eaten and the pericarp is used to treat skin diseases, remove tan, and freckles. The seed is also used to treat periodontal abscesses. In Burma, the fruits are used to treat epilepsy. In Taiwan, the flowers are used for heal inflamed eyes. In India, the plant is used to wash hair and delicate silk. In Malaysia, the plant is used as expectorant. The plant abounds with saponins and tannins, hence the anti-septic, anti-inflammatory, cosmetic, and expectorant properties mentioned earlier (96,97). Much less is known about the CNS properties of this plant, especially the anti-epileptic properties. Surprisingly, the physiopathology of epilepsy is poorly understood and so far, there is no clear association between the abnormal function of a specific group of neurons and the genesis of seizures, but Birioukova et al. made the interesting observation that the densities of D₁ and D₂ dopaminergic receptors were different in the striatum of rats with and without genetic predisposition for epilepsy (98). Is *Sapindus mukorossi* Gaertn., and the genus *Sapindus* in general, holding dopaminergic principles of value for the treatment of epilepsy?



Fig. 71. *Sapindus mukorossi*.

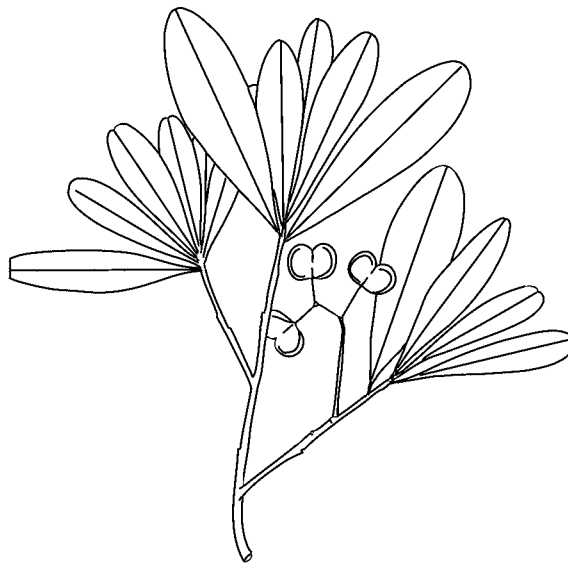


Fig. 72. *Dodonaea viscosa* (L.) Jacq. From Singapore Field No 37952. Distributed by the Botanic Gardens Singapore. Geographical localization: Kedah near Sanitarium Langkawi, in sand near sea. Date: 11/13/ 1941. Field collector: J.C. Naeur. Botanical identification: M.R. Henderson.

***Dodonaea viscosa* (L.) Jacq.**, or Florida hop bush, or *seringan laut* (Malay), is a shrub that grows to a height of 6 m in the sandy shores of the tropical world, including Asia and the Pacific Islands. The leaves are simple, 7.5–12 cm × 2 cm × 3.6 cm. The fruits are 2 cm long, capsular, and dehiscent to expose one to two black seeds in each lobe (Fig. 72).

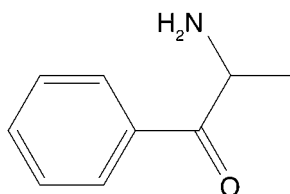
In Burma, the leaves are used in fomentations. In Taiwan and Palau, the leaves are used to treat eczema, ulcers, and to mitigate fever.

The antipyretic property of the plant is not confirmed yet, but Amabeoku et al. reported that an aqueous extract of *Dodonaea angustifolia* L. reduced fever induced by lipopolysaccharide in rodent (98). The principle involved here is unknown and one might think of 5,7,4,9-trihydroxy-3,6-dimethoxyflavone, which abounds in that plant (99). Flavonoids are able to interact with the dopaminergic system. Is the antipyretic property of *Dodonaea* species the result of flavonoids via the dopaminergic control of the hypothalamic thermoregulation? What is the antipyretic potential of 9-trihydroxy-3,6-alkylethoxy flavone in general (Fig. 74)?

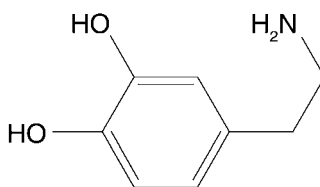
Pataki et al. showed that apomorphine and bromocriptine enhanced the elevation of body temperature induced by pituitary adenylate cyclase-activating polypeptide in rats and observed that hyperthermia was antagonized by haloperidol, suggesting the involvement of the dopaminergic system (100).

Medicinal Celastraceae

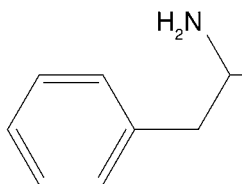
The family Celastraceae consists of about 50 genera and 800 species of trees, shrubs, or climbers known to produce a series of phenethylamine alkaloids that might hold some potentials as sources of dopaminergic agents. About 30 plant species of Celastraceae are medicinal in the Asia-Pacific region.



Cathinone



Dopamine



Amphetamine

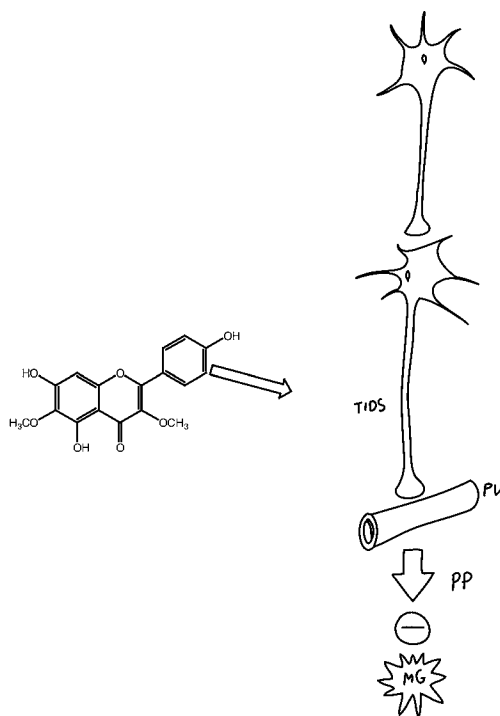


Fig. 73. Hypothetical antipyretic mechanism of 5,7,4,9-trihydroxy-3,6-dimethoxyflavone.

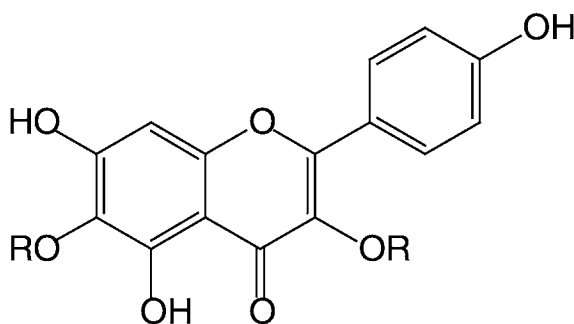
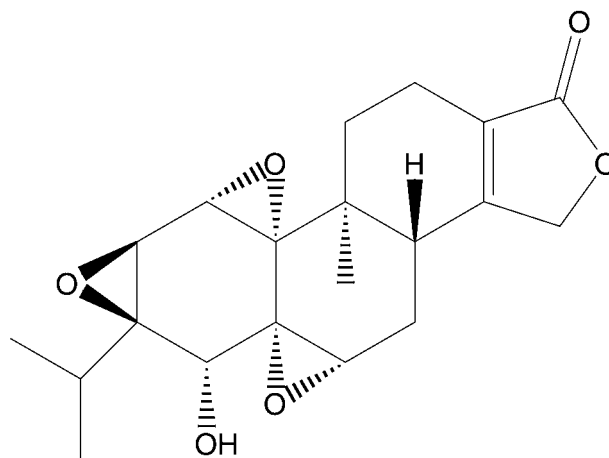


Fig. 74. 9-Trihydroxy-3,6-alkylethoxy flavones: possible antipyretic principle?

A classic example of neuroactive Celastraceae is *Catha edulis* Forsk., or *Khat*, the leaves of which are used daily by millions in a number of African and Arab countries to invigorate the intellect and to assuage hunger. Mounting evidence suggests that that (+)amphetamine and (–)cathinone produce their central stimulant effect via the same dopaminergic mechanism by increasing the levels of dopamine in the brain by acting on the catecholaminergic synapses (101,102).

***Tripterygium wilfordii* Hook f.** (*Tripterygium hypoglaucum*, *Tripterygium forrestii* (Loes.). or thunder God vine or *lei gong teng* (Chinese). is a climber that can reach a length of 10 m from East Asia to South China to Burma. The leaves are simple, crenate-ovate to elliptic, 5–15 cm × 2.5–7 cm. The flowers are whitish with five petals and 9 mm across. The fruits are three-winged and brownish red (Fig. 75).

In China, the plant is used to treat rheumatic inflammation. The anti-inflammatory property is substantiated, and a surprising amount of evidence is available. Note that the main anti-inflammatory principle of *Tripterygium wilfordii* is a diterpene triepoxide known as triptolide, which possesses potent anti-inflammatory and immunosuppressive properties (103,104).



Triptolide

Some evidence suggests glial-mediated inflammation as a possible origin for Parkinson's disease via activation of microglia that release nitric oxide, proteases, and pro-inflammatory cytokines (105). Feng-Qiao et al. made the interesting observation that triptolide concentration dependently attenuated lipopolysaccharide-induced decrease in [³H] dopamine uptake and loss of tyrosine hydroxylase-immunoreactive neurons in primary mesencephalic neuron/glia mixed culture (106). This result suggests that triptolide may protect dopaminergic neurons from lipopolysaccharide-induced degeneration.

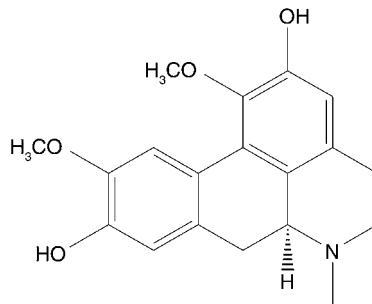
Medicinal Lauraceae

The evidence in favor of dopaminergic alkaloids from members of the family Lauraceae is strong and it seems likely that dopaminergic agents of clinical value might be characterized from this family, and to the Magnoliales–Laurales group in general, where isoquinoline abounds. Examples of such alkaloids are boldine and glaucine, which displace specific striatal [³H]-SCH 23390 binding in vitro. In vivo, glaucine at a dose of

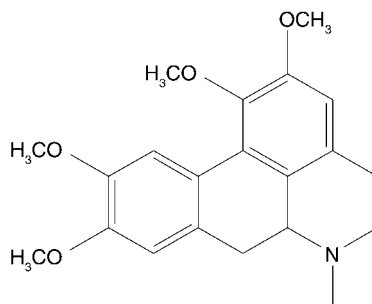


Fig. 75. *Tripterygium wilfordii* Hook f.

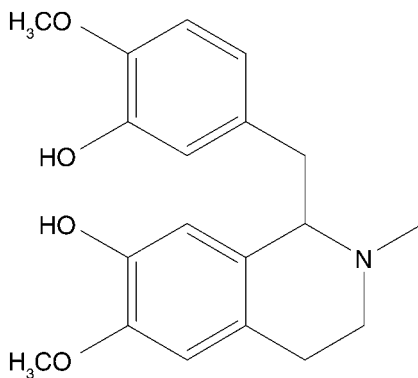
40 mg/kg (intraperitoneal) abrogates climbing, sniffing, and grooming elicited by apomorphine in mice (107). In addition, halogenation of boldine in carbon 3 leads to increased affinity for rat brain D_1 -dopaminergic receptors with some selectivity over D_2 receptors, suggesting that a 2-hydroxy group on the aporphine skeleton may determine a binding mode favoring D_1 -like over D_2 -like receptors (108). An additional example of a dopamine receptor-blocking alkaloid is reticuline, which is found in *Ocotea* species.



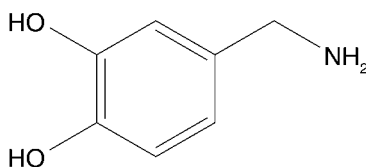
Glaucine



Boldine



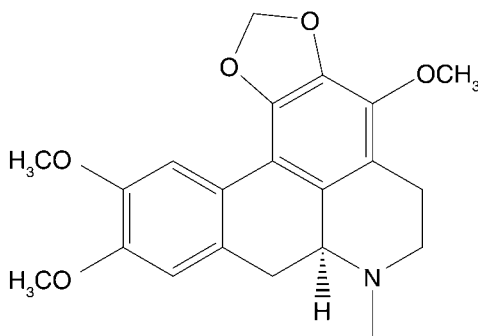
Reticuline



Dopamine

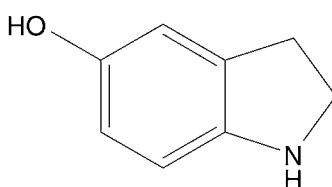
This benzylisoquinoline alkaloid inhibits *in vitro* the specific bonding of [³H] dopamine to dopamine receptors and abrogates amphetamine-induced circling behavior in rodents with unilateral degeneration of dopaminergic neurons in the corpus striatum (109).

***Cassytha filiformis* L.** (*Cassytha guinensis* Schum.), or dodder-laurel, snotty-gobble, devil's gut, or *chemar batu* (Malay), is a slender epiphytic climber common on the seashores of Africa and the Asia–Pacific region. At first glance, the plant looks like a bunch of threads, but a closer observation reveals fleshy stems, tiny yellowish flowers, and whitish berries. In Malaysia, the plant is used to promote the growth of hair. Indonesians use the plant internally as vermifuge and laxative. In the Philippines, a decoction of the fresh plant is drunk to precipitate childbirth and to remove blood from saliva. In Taiwan, the stems are used as a diuretic and emmenagogue. In Vietnam, the plant is used to treat syphilis and lung diseases. The plant is known to elaborate series of aporphine alkaloids, including ocoteine, an α_1 -adrenoreceptor antagonist.

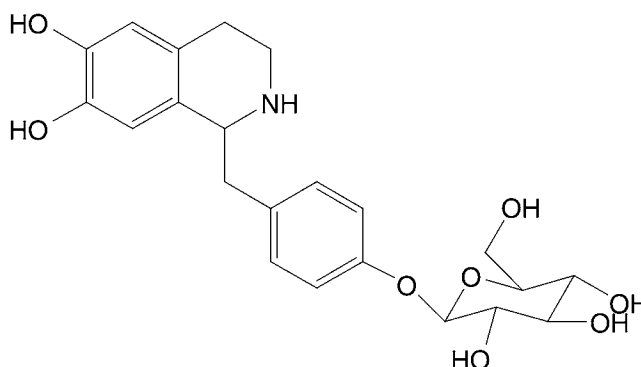


Ocoteine

The plant is known elaborate series of aporphines alkaloids such as glaucine and boldine. Glaucine is cytotoxic against HeLa cells with an IC_{50} value of $8.2 \mu\text{M}$ thought a cellular mechanism which involves DNA intercalation (110). If the cytotoxic potentials of *Lauraceous aporphines* are well-known, much less evidence is available on their dopaminergic potentials. Hegde et al. made the interesting observation that 5-hydroxy-indoline, a glycosylated tetrahydroisoquinoline analog SCH 71450 from the fruit of *Phoebe chekiangensis*, showed dopaminergic effects, in receptor ligand-binding assay for D_4 receptor (111) binding displacement.



5-Hydroxy -indoline



SCH 71450

Is *Cassytha filiformis* L. holding some potential as a source of drugs for the treatment of Parkinson's disease?

***Cryptocarya griffithiana* Wight** is a tree that grows to a height of 20 m in the lowland rainforests of Burma, Thailand, Malaysia, the Philippines, and Indonesia. The stems are stout and covered with a rusty tomentum. The leaves are simple, spiral, exstipulate, leathery, elliptic, and up to 32 cm long. The fruits are globose, glossy, and green (Fig. 76). The bark of this plant has the reputation among Malays and Indonesians of being poisonous.

The pharmacological potential of this tree is unexplored. Note that *Cryptocarya* species are very interesting, as they have the tendency to elaborate a series of stilbenes derivatives known as α -pyrones (112,113). The neuropharmacological potential of such

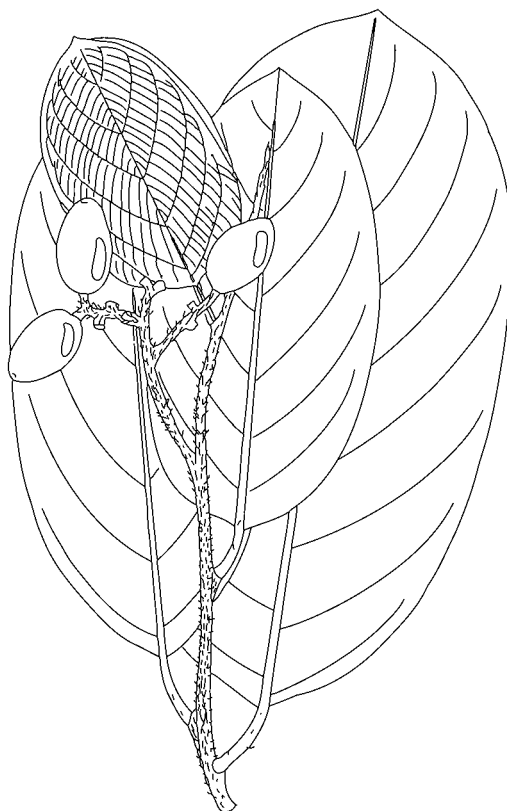
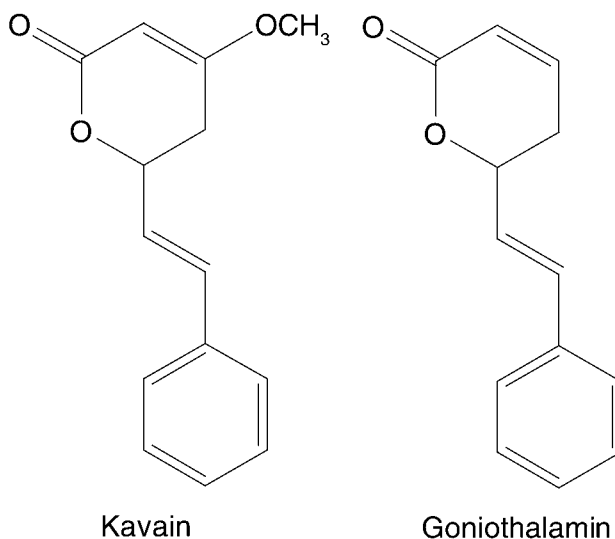


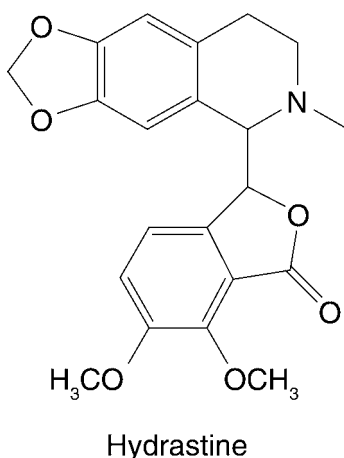
Fig. 76. *Cryptocarya griffithiana*. Distributed by The Botanic Gardens, Singapore, Malay Peninsula. Geographical localization: Kayu River, East Johor, low altitude. 3/9/1937. Det. M.H. Henderson, FSP Ng.

compounds would probably be worth assessment because α -pyrones are known for their anxiolytic properties. Examples of such agents are kavapyrones from a Piperaceae, *Piper methysticum* Forst. (kava, *British Pharmaceutical Codex*, 1934) or *kava-kava*, the rhizomes of which have been used since early times by Polynesians to allay anxiety. Kava is commercially available for relaxation. Baum et al. observed that a small dose of kava extract (120 mg/kg intraperitoneal per kilogram of body weight) caused changes in the normal behavior of rats and increased concentrations of dopamine in the nucleus accumbens (114). In addition, Matsumoto et al. recently suggested the possible involvement of cortical GABA neuronal mechanisms in the regional differences of dopamine response to psychological stress, and found that GABAergic neuronal system in the prefrontal cortex plays a key role in the regional differences of the dopaminergic response to psychological stress (115). Are α -pyrones dopaminergic via GABAergic modulation?



Medicinal Ranunculaceae

Some preliminary evidence has already been presented indicating that alkaloids of Ranunculaceae as a possible source for dopaminergic agents. This large family is classically known to hold a very large amount of ornamental, but drastically poisonous, herbs including for instance *Ranunculus acris* (buttercup), *Helleborus niger* (Christmas rose), *Adonis vernalis* L., *Aquilegia vulgaris*, and *Helleborus orientalis*. Diterpene alkaloids, such as aconitine, elatine, and delphinine, induce tingling of the tongue, mouth, stomach, and skin followed by numbness, anesthesia, nausea, vomiting, diarrhea, excessive salivation, incoordination, muscular weakness, vertigo, and death from paralysis of the heart or the respiratory center. Classic examples of ranunculaceae alkaloids are berberine and hydrastine.



Aconitum fischeri Reichb., or fischer's monkshood, American aconite, *bao ye wu tou*, or *wu tou* (Chinese), is an herb that grows to a height of 1.6 m tall in China, Korea,

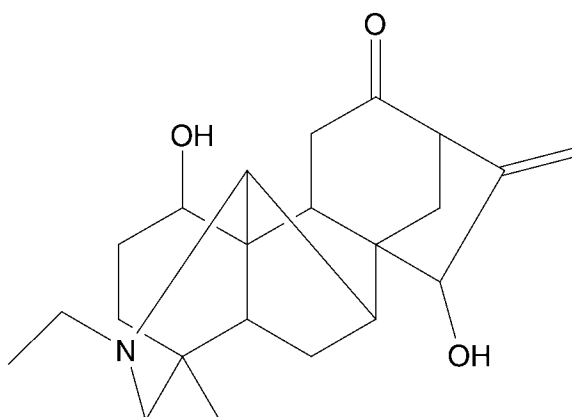


Fig. 77. *Aconitum fischeri* Reichb.

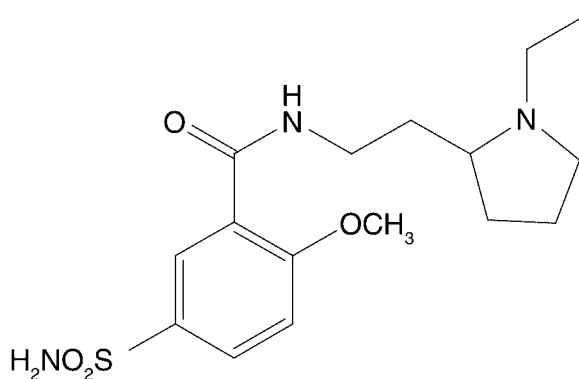
Russia, and the Rocky Mountain region of the United States. The stem is erect and pubescent at apex. The leaves are orbicular $8\text{--}12 \times 12\text{--}15$ cm and deeply three- to five-lobed. The flowers are arranged in racemes, deep blue color, 8 mm long, with a spur that is slightly circinate. The fruits are 1.4 cm long follicles (Fig. 77). The drug consists of the dried rhizome. In China, the rhizome is used to treat cold, cause abortion, and as a treatment for lumbago, pox, and ulcers.

The pharmacological potential of this herb is currently unexplored. One might set the hypothesis that the plant contains aconitine and other diterpene alkaloids, such as songorine, which is common in the *Aconitum* species. Interestingly, songorine, is a non competitive antagonist at the GABA_A receptor, which inhibits the specific binding of [³H]muscimol to GABAergic receptors with an IC₅₀ value of 7.06 mM (116). Using electrophysiological methods, Ameri showed that songorine (1–100 μM) enhances the excitatory synaptic transmission by agonistic action at D₂ receptors (117). This effect is

completely abolished by the selective dopamine D₂ receptor antagonists sulpiride (0.1 μM) and haloperidol (10 μM) and mimicked by amantadine (100 μM).



Songorine

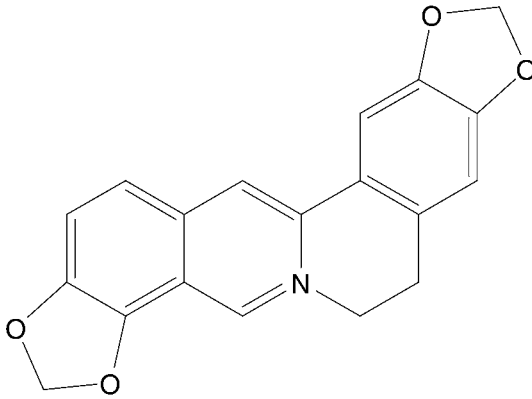


Sulpiride

***Coptis teeta* Wall.** (*Coptis chinensis* Franch, *Coptis teeta* Wall. var. *chinensis* Franch.), or Indian goldthread, *yun nan huang lian*, *wang lien*, or *chih lien* (Chinese), grows wild in China and is cultivated in Szechuan. It is an herb that grows to a height of 50 cm from a rhizome. The petioles are up to 19 cm glabrous and the blade is ovate-triangular, 6–13 cm × 6–9 cm, and membranaceous. The fruits are papery follicles of about 1 cm long (Fig. 78). The drug consists of the roots, which are said to have a bird's claw appearance. It is bitter, yellow within, and aromatic. In China, the plant is used to soothe inflamed eyes, reduce fever, treat dysentery and diabetes, promote digestion, and counteract poisoning. The root is given to newborns to prevent syphilitic poisoning and mouth sores. In Cambodia, Laos, and Vietnam, the root is used to treat leucorrhoea, promote menses, heal mouth sores and ulcers, and treat conjunctivitis. The root abounds with berberine and coptisine, which impart to the plant most of its medicinal properties.



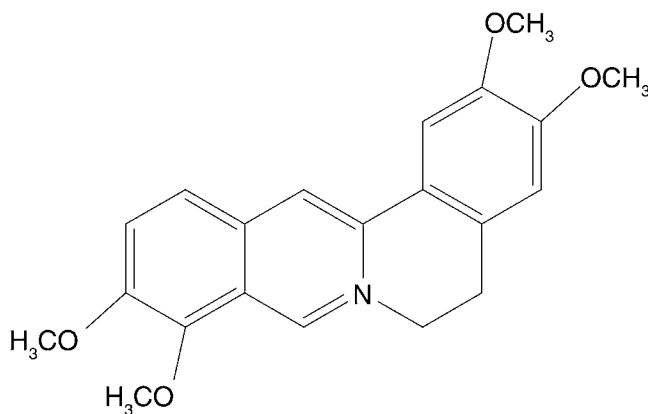
Fig. 78. *Coptis teeta* Wall.



Coptisine

The plant is regarded as a sort of panacea by Chinese doctors, and has attracted a great deal of interest for its cytotoxic and antibacterial properties. The plant was a source of berberine sulphate (*British Pharmacopoeia*, 1949) that was given orally as bitter and in India parenterally for the treatment of oriental sore. Berberine inhibits the enzymatic activity of sortase, with an IC_{50} value of $8.7 \mu\text{g/mL}$, and exhibits antibacterial activity against Gram-positive bacteria and could be of value as a source of clinical antiperiodontobacterial agent (118).

Coptis chinensis abrogates the survival of a broad spectrum of cancerous cell-lines—SK-Hep1, HepG2, and Hep3B—and berberine and coptisine inhibit the proliferation of both hepatoma and leukemia cell lines, with IC_{50} values ranging from 1.4 to $15.2 \mu\text{g/mL}$ and from 0.6 to $14.1 \mu\text{g/mL}$, respectively. However, icariin showed no inhibition of either the hepatoma or leukemia cell lines. An extract of *Coptis chinensis* is cytotoxic against a broad spectrum of cancerous cell-lines—SK-Hep1, HepG2, and Hep3B—and berberine and coptisine have potent antineoplastic properties (119). Note that the anti-inflammatory property of the plant is confirmed, as an extract of the plant exhibited free radical scavenging activity (120). Both the cytotoxic and antibacterial properties are known, but much less work has been done however on the dopaminergic potentials of this herb and the genus *Coptis* in general.



Palmatine

Lee et al. made the first observation that protoberberine alkaloids from *Coptis japonica* Makino, such as berberine and palmatine, induced 77% inhibition on dopamine content in PC12 cells with IC_{50} value of $19.5 \mu\text{g/mL}$, and inhibited the biosynthesis catalyzed by tyrosine hydroxylase in PC12 cells with IC_{50} values of berberine and palmatine of 9.5 and $7.7 \mu\text{g/mL}$, respectively, indicating that the *Coptis* species—and possibly other protoberberines—and *sensu lato* isoquinoline-containing plants might play some role in the etiology of Parkinsonism (121). It is again interesting to note that both dopaminergic and anti-dopaminergic principles coexist in the same taxonomic group.

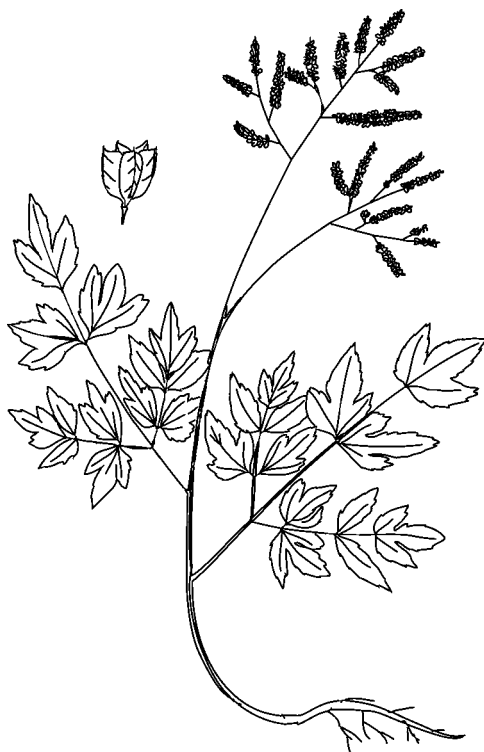
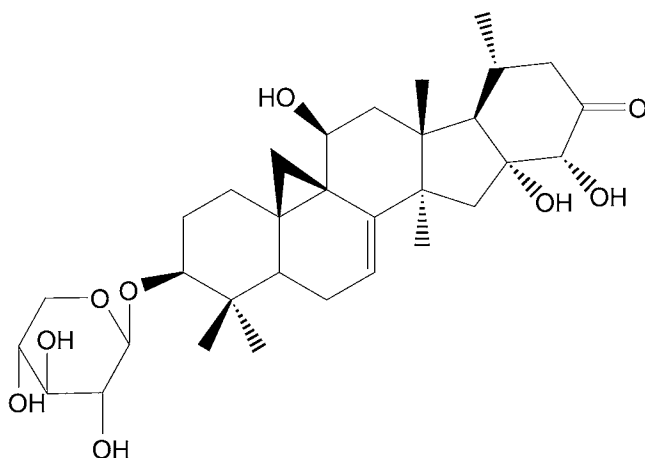


Fig. 79. *Cimicifuga foetida* L.

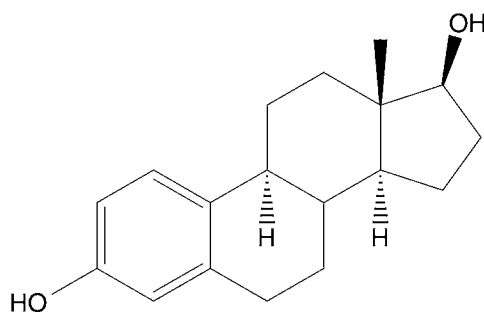
Surprisingly, *C. chinensis* attenuated the scopolamine-induced amnesia in rats when given orally for 1 week (122).

What is the role of dopamine on memory? The dopamine D_3 receptor has been extensively studied in animal models of drug abuse and psychosis; however, less is known of its possible role in cognitive functions. Laszy et al. investigated the effects of different D_3 antagonists and a partial agonist on spatial learning performance in a water labyrinth test, and clearly demonstrated that D_3 antagonists, such as SB-277011 (24 mg/kg orally) attenuated the memory impairments caused by FG-7142, suggesting that dopamine D_3 receptor antagonists have potentials in improving cognition associated with several psychiatric disorders (123).

***Cimicifuga foetida* L.**, or *sheng ma* (Chinese), is an herb that grows from a rhizome to a height of 2 m in China, Bhutan, India, Kazakhstan, Mongolia, Burma, and Siberia. The leaves are pinnate; the petiole grows up to 15 cm long; and the leaf blade is lobed and serrate. The flowers are 4 mm in diameter and the petals are broadly elliptic. The fruits are 8–14-cm \times 2.5–5-mm follicles (Fig. 79). The drug consists of the rhizome, which is used to treat headaches, sore throat, dysentery, measles, smallpox, ulcers, antidotal, and calming in China. The pharmacological potential of this plant is, to date, unveiled. Note that the plant elaborates a series of triterpenoid saponins and original cycloartane triterpenes, such as neocimicidine of the cycloartane (124,125).



Neocimicidine



Oestradiol

Note that the dried rhizome of *Cimicifuga racemosa* (*British Pharmaceutical Codex*, 1934; black cohosh) has been used as a bitter and mild expectorant in the form of a liquid alcoholic extract (1 in 1; dose: 0.3–2 mL) and is sold as alternative remedy for the treatment of menopausal syndrome at dose of 40–80 mg/day. The active constituents of black cohosh, and, therefore, the precise molecular mechanism of action involved in the climacteric property of *Cimicifuga racemosa*, are still unknown. The most recent data suggest that the plant is not estrogenic *sensu stricto* (126).

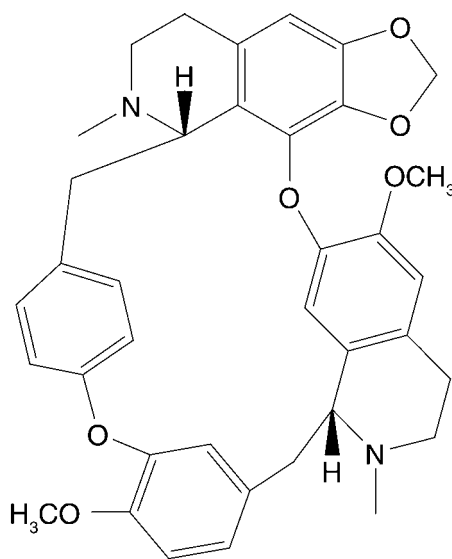
Jarry et al. showed that the extract of *Cimicifuga racemosa* contains some agents that bind to an unknown estrogen-binding site in the endometrium and dopamine D₂ receptors (127). It will be interesting to learn whether further study on *Cimicifuga foetida* and the *Cimicifuga* species disclose any dopaminergic principles, and whether these are isoquinoline alkaloids. What is the interrelationship between estrogens and dopamine? Can we expect estrogenic compounds as antiparkinson agents?

Medicinal Menispermaceae

The family Menispermaceae consists of 70 genera and about 400 species of tropical climbers that have attracted a great deal of interest on account of their ability to elaborate

a series of benzylisoquinoline and aporphine alkaloids. The cardinal features of Menispermaceae are the transversal section of the stem, which shows a yellow wood with broad medullary rays, and muricate and horseshoe-like seeds in glossy little berries. In regard to the pharmaceutical usefulness of Menispermaceae, the dried transverse slices of roots of *Jateorrhiza palmata* Miers (calumba, *British Pharmaceutical Codex*, 1954) and the dried stems of *Tinospora cordifolia* (tinospora, *Indian Pharmaceutical Codex*) have been used to promote appetite and digestion. Examples of drugs obtained from Menispermaceae are picrotoxin and tubocurarine. Tubocurarine, from curare-producing Amazonian Menispermaceae, is anticholinergic at the neuromuscular synapse and abrogates the tone of skeletal muscles, hence its use in general anesthesia (tubocurarine chloride, *British Pharmacopoeia*, 1963).

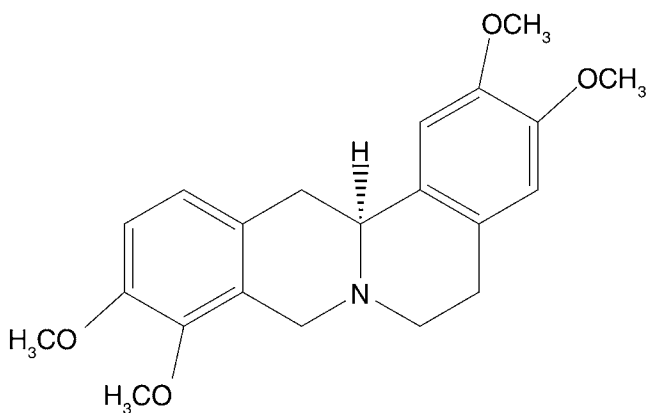
About 40 plant species in this family are medicinal in the Pacific Rim. Note that many of these are used to reduce fever, promote urination and digestion, and mitigate pains. Although there have been many studies on the phytochemical constituents of Menispermaceae, much less work has been done on the central nervous potential of these isoquinoline-producing plants. An interesting development from Menispermaceae is the search for dopaminergic agents because preliminary evidence suggests that alkaloids such as tetrahydropalmatine bind to dopaminergic D_2 receptors (128).



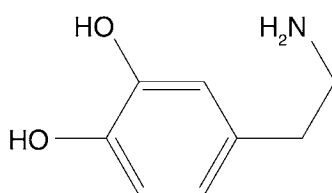
Cepharrantine

***Stephania cepharantha* Hayata** (*Stephania tetrandra* S. Moore var. *glabra* Maxim.; *Stephania disciflora* Handel-Mazzetti), or *jin qian diao wu gui* (Chinese), is a climber that grows to 2 m long in open fields and forest edges of China and Taiwan. The roots are tuberous. The stems are purplish-red and prominently lenticelled. The leaves are simple, exstipulate, membranaceous, triangular, and 2–6 cm × 2.5–6.5 cm. The apex of the blade is finely mucronate. The flowers are minute. The fruits consist of drupes that are broadly rotund and 6.5 mm long. In Taiwan, the roots are used to treat epilepsy.

The plant is known to contain cepharantine, which has attracted a great deal of interest on account of its ability to induce apoptosis, fight lung metastasis, and inhibit the replication of HIV (129–131).



Tetrahydropalmatine



Dopamine

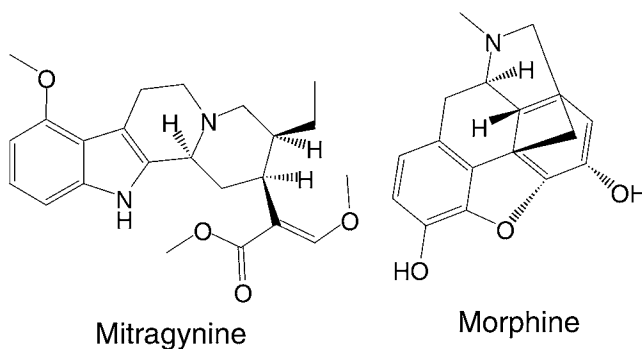
The antiepileptic property of the plant is, however, not substantiated experimentally yet. Vauquelin et al. observed that (\pm)tetrahydropalmatine binds to dopaminergic D₁ and D₂ dopaminergic receptors in membranes from human putamen (128). Hu et al. noted that intraperitoneal injection of tetrahydropalmatine, as well as D₂ receptor antagonist spiperone, produced dose-dependent antinociceptive effects on the nociception of rats, and suggested that activating the spinal D₂ receptor or blocking the supraspinal D₂ receptor produces antinociception (132). In addition, tetrahydropalmatine abrogates the increase of amygdaloidal release of dopamine in rats treated with 3 mg of picrotoxin per kilogram parenterally (133). The question arises, therefore, whether *Stephania cepharantha* Hayata is antiepileptic through inhibition of amygdaloid dopamine release or not, and if it is, what is the active principle?

CONCLUSION AND FUTURE PROSPECTS

In conclusion, a massive body of evidence has been presented to show that the medicinal plants of the Pacific Rim hold serious potential as source of drugs for the treatment of CNS-related disorders. In summary, the most remarkable feature is

the taxonomical and chemical diversity of these drugs. Given the number of medicinal plants in the Pacific Rim, the number of molecules with effects on the CNS is likely to expand in the future, and it is vital to establish a systematic neuropharmacological investigation of these plants *in vitro* and *in vivo*. It is likely that in the near future methods will be developed to assess more efficiently the CNS properties of plant secondary metabolites, including *in vitro* cultures of neurones or neuronal systems and even brains. The availability of original natural products together with the techniques for studying the affinity of plant products to receptors, will contribute significantly to the discovery of centrally active agents. In addition to the knowledge pertinent to the major neuronal systems, one may eventually begin to conceive of strategies for the control of diseases in which serotonin, GABA, glycine, and dopamine, and as of yet unveiled neurotransmitters. In regard to the taxonomic distribution, it appears that alkaloid-producing families are the predominant source of CNS-acting agents, especially in the Magnoliidae and Asteridae (134). One wonders if other sorts of plant metabolites have been skipped.

Note that the families Rubiaceae, Solanaceae, and Convolvulaceae are known to elaborate a series of neuroactive alkaloids, some of clinical value, and represent an interesting pool of potentially centrally active agents. The Rubiaceae in particular has attracted a great deal of interest on account of *Mitragyna speciosa*, from which mitragynine has been characterized, an indole alkaloid of possible value for the treatment of opioid dependence. Górnjak et al. studied the effects of *Palicourea marcgravii* (Rubiaceae) leaf on dopamine related behaviors in rats and made the interesting observation that the extract given had a blocking action on a mesostriatal dopamine receptor (135). In the Convolvulaceae–Solanaceae group, some evidence currently available suggests the presence of GABAergic principles. The methanolic extract of stem of *Cuscuta reflexa* (Convolvulaceae) protected rodents against convulsion induced by chemoconvulsive agents in mice, and increased the levels of dopamine and, surprisingly, of GABA in mice brain after a few weeks (136).



Much less work has been done in the Caryophyllidae, Dilleniidae, and Rosidae. In the Rosidae, the family Anacardiaceae would be worth studying for GABAergic activity

because Risa et al. observed that extracts of *Rhus tridentate* and *Rhus rehmanniana* are traditionally used to treat epilepsy and convulsions in South Africa, and they have good dose-dependent activity in the GABA_A-benzodiazepine receptor binding assay (137). Other Rosidae of interest are Crassulaceae, where *Bryophyllum pinnatum* produced a dose-dependent prolongation of onset and duration of pentobarbitone-induced hypnosis, reduction of exploratory activities in the head-dip and evasion tests in rodents, and delayed onset to convulsion in both strychnine- and picrotoxin-induced seizures (138). Note that Caryophyllidae is still unexplored and the question arises as to whether peptides and oligosaccharides active on the CNS await discovery in this vast taxon.

The evidence for the existence of psychopharmaceutical principles in the Liliopsida is strong, and it seems likely that further research on neuroactive substances from the monocots might pay off sooner or later. An interesting development from Liliopsida is the search of GABAergic and dopaminergic agents from Orchidaceae and Araceae, respectively. A water extract of the dried rhizome of *Acorus gramineus* Soland. dose-dependently inhibits the locomotor activity and the intensity of apomorphine-induced stereotypic behavior, and potentiates pentobarbital-induced sleeping time in rodents at dose 0.5–5.0 g/kg. Receptor binding assays showed that the extract displaced [³H]SCH-23390 and [³H]YM-09151-2 for specific binding to striatal dopamine D₁ and D₂ and competed with [³H]muscimol for specific binding to the GABA binding site of cortex GABA_A receptors (139).

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