BOTANY, USES, PHYTOCHEMISTRY AND MEDICINAL PROPERTIES OF SELECTED APOCYNACEAE SPECIES

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Keywords: *Calotropis gigantea*, *Cascabela thevetia*, *Catharanthus roseus*, *Cerbera odollam*, *Kopsia fruticosa*, *Nerium oleander*, *Plumeria rubra*, *Tabernaemontana divaricata*, *Vallaris glabra*

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Summary

Apocynaceae is a very large plant family of trees, shrubs and vines in the tropics and subtropics. Most species produce a milky sap that is often poisonous. Flowers are large, colorful, bisexual and fragrant with five contorted lobes. The family has been enlarged from two to five sub-families. In traditional medicine, Apocynaceae species are used to treat fever, malaria, pain, diabetes and gastrointestinal ailments, including skin and parasitic infections. Non-medicinal purposes include food, poisons, fodder, wood, ornamentals, dye and perfume. Many species are planted as ornamentals in gardens, parks and along roadsides. Some species are trees that are an important source of wood. Flowers of some species are used for prayers or are woven into garlands or wreaths. Major classes of metabolites of Apocynaceae plants are alkaloids and cardenolides. Other classes include flavonoids, iridoids, phenolic acids and terpenoids. Alkaloids and cardenolides of Apocynaceae have wide-ranging bioactivities and pharmacological properties including anticancer effects.

In this chapter, the phytochemistry and medicinal properties of nine Apocynaceae species belonging to nine genera are reviewed. *Cascabela thevetia*, *Catharanthus roseus*, *Cerbera odollam*, *Kopsia fruticosa*, *Plumeria rubra* and *Tabernaemontana divaricata* belong to the sub-family Rauvolfioideae. *Nerium oleander* and *Vallaris glabra* are of the sub-family Apocynoideae while *Calotropis gigantea* is the only species of the sub-family Asclepiadoideae. The toxicity of *C. thevetia*, *C. odollam* and *N. oleander* is also discussed. The phytochemistry of selected Apocynaceae species is focused on cytotoxic alkaloids or cardenolides. Medicinal properties are focused on anticancer activities of extracts and compounds.

1. Apocynaceae

1.1. Botany and Uses

Apocynaceae is a large plant family of trees, shrubs and vines that produce a milky sap. Species are mostly found in the tropics and subtropics. Leaves are simple, opposite or whorled. Flowers are bisexual, large, colorful and fragrant with five contorted lobes. Fruits are a drupe, berry, capsule or follicle, occurring in pairs. With the inclusion of species of Asclepiadaceae, the Apocynaceae family has been enlarged from two to five sub-families, namely, Apocynoideae, Asclepiadoideae, Periplocoideae, Rauvolfioideae and Secamonoideae. The expanded family now comprises almost 380 genera and more than 5,350 species.

In traditional medicine, Apocynaceae species are used to treat fever, malaria, pain, diabetes and gastrointestinal ailments, including skin and parasitic infections. The bark of *Alstonia* contains alkaloids that are used as substitute for quinine to treat malaria. Non-medicinal purposes include food, poisons, fodder, wood, ornamentals, dye and perfume. Many species are planted as ornamentals in gardens, parks and along roadsides. Some species are trees that are an important source of wood. The creamy white and fine textured wood of *Dyera* is suitable for panelling, and in the manufacture of products such as pencils, match sticks, carvings and other wooden accessories. The light and soft timber of *Alstonia* has been used to make coffins, floats, corks, packing boxes, match sticks, carvings, writing tablets and household utensils. Flowers of Tabernaemontana are plucked by Hindus in the morning for prayers. Flowers of Plumeria are woven into garlands or wreaths.

1.2. Classes of Metabolites

In Apocynaceae plants, major classes of metabolites are alkaloids and cardenolides. Other classes include flavonoids, iridoids, phenolic acids and terpenoids.

1.2.1. Alkaloids

Alkaloids are one of two major classes of metabolites in Apocynaceae. They are a highly diverse group of compounds that contain a heterocyclic ring structure with the presence of a N atom as the unifying feature. Most alkaloids possess one nitrogen atom, but some can have up to five. The nitrogen may occur in the form of a primary, secondary or tertiary amine. Besides carbon, hydrogen and nitrogen atoms, most alkaloids contain oxygen atoms. Alkaloids can occur as monomers, dimers, trimers or tetramers.

Alkaloids can be divided into two broad divisions. Heterocyclic or typical alkaloids contain nitrogen in the heterocycle. Non-heterocyclic or atypical alkaloids (also known as proto-alkaloids) that contain nitrogen in a side chain. Most alkaloids are assigned names that end with the letters ‘ine’ and are named after the plant species. Examples are kopsine and fruticosine are alkaloids of *Kopsia fruticosa*, and alstonine and angustilobine are alkaloids of *Alstonia angustiloba*. Alkaloids are also named after their geographic location of origin, their pharmacological activity or their discoverers.

Alkaloids are normally classified according to the heterocyclic ring system they possess e.g., indole, isoquinoline, quinoline, piperidine, pyridine and pyrrolidine alkaloids. Sometimes, alkaloids are classified under their respective genera they are isolated e.g., *Alstonia*, *Catharanthus*, *Kopsia*, *Rauvolfia* and *Tabernaemontana* alkaloids.

Among five plant families (Apocynaceae, Fabaceae, Papaveraceae, Ranunculaceae and Rutaceae) rich in alkaloids, Apocynaceae is the richest with more than 2,660 alkaloids isolated from 400 species belonging to 76 genera. Indole, bisindole, ibogan, steroidal, vallesamine and vinca alkaloids are often reported in Apocynaceae, notably from species of the genera *Allamanda*, *Catharanthus*, *Kopsia*. *Rauvolfia*, *Strophanthus* and *Tabernaemontana*. Many types of indole alkaloids are found in Apocynaceae. They include β-carboline, monomeric, monoterpene and terpenoid indole alkaloids. Steroidal alkaloids are also found in Apocynaceae.

1.2.2. Cardenolides

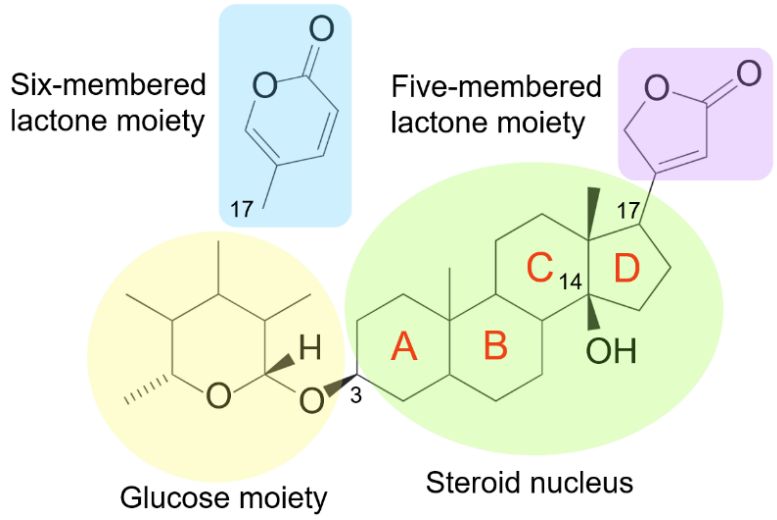


Figure 1. Molecular structures of cardenolide with five-membered lactone moiety and bufadienolide with six-membered lactone moiety

Cardenolides are C_{23} steroids consisting of a steroid nucleus, a five-membered unsaturated lactone moiety (butyrolactone ring) at C17 and an −OH group at C14 (Figure 1). The glycones of cardenolides have a sugar moiety at C3 comprising one to three monosaccharide units. In Apocynaceae, species of the genera *Calotropis*, *Cascabela*, *Cerbera*, *Nerium* and *Strophanthus* are the major sources of cardenolides. In Apocynaceae, cardenolides are recorded in 76 species and 33 genera.

Cardenolides and bufadienolides are two main classes of cardiac glycosides. Bufadienolides are C_{24} steroids and structurally differ from cardenolides by having a six-membered α-pyrone ring. They also have an −OH group at C14 and typically have a sugar moiety at C3. Not found in Apocynaceae, bufadienolides have been recorded in 21 species, nine genera and six families. Pregnanes are biological precursors of cardenolides. They are C_{21} steroids with four fused rings, methyl groups at C10 and C13,

and an ethyl side chain at C17. Pregnane glycosides occur alongside cardenolides in many Apocynaceae species.

1.3. Pharmacological Activities

Alkaloids of Apocynaceae have wide-ranging bioactivities and pharmacological properties. Over one-third are pharmaceutically significant. Pharmacological activities of alkaloids from selected genera of Apocynaceae are listed in Table 1.

Plant genus	Pharmacological Activity
Alstonia	Antibacterial, anticancer, antidiabetic, antidiarrheal, antifertility, antifungal, anti-HIV, anti-inflammatory, antipsychotic, antimalarial and vasorelaxant
Catharanthus	Antibacterial, anticancer, antifungal, anti-HIV, antihyperglycemic, anti-inflammatory, anti-plasmodial, anti-plasmodial, hepatoprotective and wound healing
Ervatamia	AChE inhibitory, anticancer, antihyperglycemic and anti-inflammatory
Funtumia	Antibacterial, anticancer, antifungal, anti-inflammatory, anti-plasmodial and hepatoprotective
Hunteria	Anticancer, antihyperglycemic, anti-plasmodial and vasorelaxant
Kopsia	Antibacterial, anticancer, antidiarrheal, antifungal, anti-inflammatory, antileishmanial, anti-plasmodial, antitussive, cardiotonic and cardiovascular
Rauvolfia	Antiarrhythmic, antibacterial, anticancer, antidiarrheal, antifungal, anti-HIV, antihypertensive and cardiovascular
Tabernaemontana	AChE inhibitory, analgesic, antibacterial, anticancer, anticonvulsant, antidiabetic, antidiarrheal, antifertility, antifungal, antihyperglycemic, antinociceptive, antipyretic, cardiovascular, gastroprotective, hypotensive and vasorelaxant

Table 1. Biological and pharmacological activities of alkaloids from selected genera of Apocynaceae

In Apocynaceae, cardenolides possess multiple bioactivities and pharmacological properties (Table 2). Over 25% of the 109 cardenolides have been reported to possess anticancer activity involving multiple signaling pathways. Cardenolides are promising agents for cancer chemotherapy as they can induce apoptosis and inhibit the growth of cancer cell lines. The anticancer effects of cardenolides have been attributed to the sugar moieties at position C3. Ranked in decreasing order, cytotoxicity is in the order of monosaccharide > disaccharide > trisaccharide > aglycone. The anticancer activities of cardenolide glycosides are therefore stronger than that of the relative aglycones.

Plant genus	Pharmacological activity
Adenium	Antibacterial, anticancer, antiviral, larvicidal and trypanocidal
Asclepias	Analgesic, anticancer, anti-inflammatory, antipyretic and cardiovascular
Calotropis	Analgesic, antibacterial, anticancer, antifertility, anti-inflammatory, antifungal, anti-plasmodial, hepatoprotective and hypoglycaemic
Cascabela	Anticancer, anti-plasmodial, cardioprotective, gastroprotective and wound healing
Cerbera	Analgesic, anticancer, anticonvulsant, cardiotonic and hypotensive
Nerium	Anticancer, anti-HIV, anti-inflammatory, cardioprotective, CNS depressant and hepatoprotective
Vallaris	Analgesic, antibacterial, anticancer, antifungal, antioxidant, anti-ulcer and TRAIL-resistance-overcoming

Table 2. Biological and pharmacological activities of cardenolides from selected genera of Apocynaceae

2. *Calotropis gigantea*

Synonym: *Asclepias gigantea*
Common names: Crown flower, Giant milkweed
Sub-family: Asclepiadoideae

2.1. Botany and Uses

Calotropis gigantea (L.) Dryand. is a small tree that is native to South and Southeast Asia. The plant is fast-growing, drought-resistant and exudes a milky sap when bruised. Leaves of *C. gigantea* are obovate, thick, velvety, sub-sessile with light-colored veins. The upper leaf surface is smooth and velvety at the lower leaf surface. Mature leaves turn yellow before shedding. Flowers are pale purple or white and have an elaborate crown structure due to the highly modified stigma and stamens (Figure 2). Flowering is throughout the year. Fruits of *C. gigantea* are fleshy capsules, curved, horn-shaped and yellowish-brown when ripe. Fruit set is infrequent. Seeds are small with fine woolly hairs which assist in dispersal by wind.

From the many reviews of *C. gigantea*, their uses in traditional medicine are so diverse that all plant parts including the leaf, stem bark, root, flower, fruit and latex are remedy for many kinds of ailments and infections. All plant parts of *C. gigantea* have been traditionally used for the treating diseases such as leprosy, ulcers, tumors and piles. The leaves are used to treat dysentery, earaches leprosy, skin and liver diseases, tumors, ulcers and worms. Its latex has been reported to possess wound healing properties. The scientific evidence of many of these uses requires validation. Non-medicinal traditional uses include the harvesting of stem bark for making ropes and clothes. The flowers of *C. gigantea* are used by Hindus for prayers. In Hawaii and the Pacific, the residents make garlands or leis out of the flowers.

Figure 2. *Calotropis gigantea* with pale purple flowers (left) and white flowers (right)

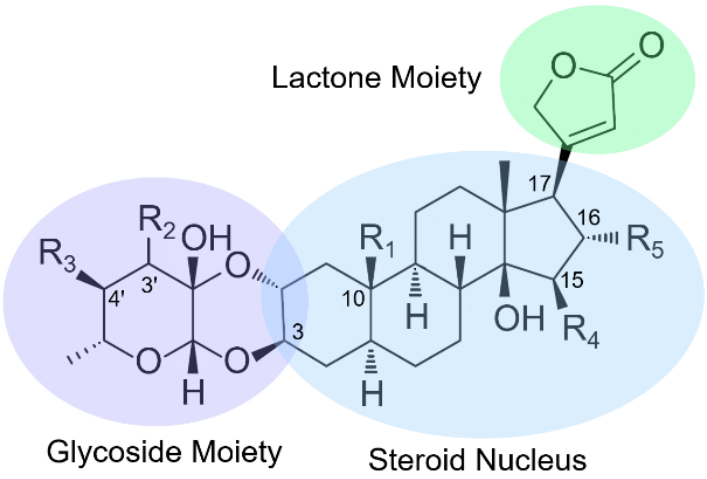
2.2. Phytochemistry

Cardenolides of *C. gigantea* included afroside, calactin, calactinic acid, calotoxin, calotropagenin, calotropin, coroglaucigenin, 19-dihydrocalactin, frugoside, gofruside, uscharin and uzarigenin. Calotropone and calotroposides A−G are pregnanes (precursors of cardenolides) isolated from *C. gigantea*.

2.3. Medicinal Properties

Many medicinal properties of *C. gigantea* have been reported. They include analgesic, anthelmintic, anti-arthritic, anti-asthmatic, antibacterial, anti-convulsant, antidiabetic, anticancer, antidiarrheal, anti-histamine, anti-inflammatory, antioxidant, anti-plasmodial, anti-pyretic, anti-ulcer, anti-venom, anti-viral, anxiolytic, cardioprotective, contraceptive, fibrinolytic, hair-growing, hepatoprotective, hypoglycemic, insecticidal, ovicidal, sedative, vasodilatory and wound healing activities.

Cardenolides of leaves, roots and stem bark of *C. gigantea* possess cytotoxic effects towards cancer cells. The methanol leaf extract has been reported to be cytotoxic towards against MCF-7 breast, A549 lung and HeLa cervical cancer cells. From the leaves, calactin and calotropin were cytotoxic towards cervical and lung cancer cells, while calotoxin and frugoside displayed cytotoxicity against oral, breast and lung cancer cells. From the roots of *C. gigantea*, calotropin and frugoside were found to have cytotoxic activity against human cancer lines but not against mouse cancer lines. Coroglaucigenin and frugoside isolated from the roots exhibited significant cytotoxic activity against K-562 leukemia and SGC-7901 gastric cancer cells. 19-Dihydrocalactin, calactin and calotropin from the root bark exhibited cytotoxicity towards A549 lung and HeLa cervical cancer cells. It has been postulated that the presence of a glycoside moiety at C3, a formyl group at C10, and a lactone moiety at C17 are crucial for the cytotoxic effects. The molecular structures of cardenolides of *C. gigantea* (afroside, calactin, calotoxin, calotropin and 19-dihydrocalactin) displaying the steroid nucleus, lactone moiety and glycoside moiety are shown in Figure 3.



Cardenolide	R_1 (C10)	R_2 (C3')	R_3 (C4')	R_4 (C15)	R_5 (C16)
Afroside	CH_3	β-OH	H	OH	H
Calactin	CHO	β-OH	H	H	H
Calotoxin	CHO	β-OH	OH	H	H
Calotropin	CHO	α-OH	H	H	H
19-Dihydrocalactin	CH_2OH	β-OH	H	H	H

Figure 3. Molecular structures of cardenolides commonly found in *Calotropis gigantea*

3. *Cascabela thevetia*

Synonyms: *Thevetia peruviana*, *T. neriifolia*, *Cerbera peruviana*, *C. thevetia*, *Cascabela peruviana*
Common name: Yellow oleander
Sub-family: Rauvolfioideae

3.1. Botany and Uses

Cascabela thevetia (L.) Lippold is a shrub with a dense crown. All parts of the plant produce a milky white sap that is toxic. Leaves are linear, dark green and glossy. They are spirally arranged along the stem. Flowers are borne in small clusters at the tip of twigs and last only for a day. They are yellow in color, large, funnel-shaped, sweetly scented and have five petals (Figure 4). Fruits are a fleshy, triangular drupe, green turning yellow and then black. They contain a stone with two seeds.

In folk medicine, *C. thevetia* has antipyretic, molluscicidal, rodenticidal and antibacterial usage. Despite its toxicity, the species has been used as an abortifacient, and to treat congestive heart failure, malaria, leprosy, indigestion, ringworm and venereal disease. The white sap of *C. thevetia* has been applied to treat wounds and skin infections.

3.2. Phytochemistry

Cardenolide glycosides are the major compounds of *C. thevetia* with the seeds having the highest content. They include acetylthevetins A−C, cerberin, neriifolin, perusitin, peruvoside, ruvoside, thevefolin, thevetins A−C, thevetiosides A, C and F, and thevetoxin.

Figure 4. Flower (left) and fruit (right) of *Cascabela thevetia*

3.3. Medicinal Properties

Medicinal properties of *C. thevetia* include anticancer, antidiabetic, antifertility, antimicrobial, antioxidant, HIV-1 integrase inhibitory, HIV-1 reverse transcriptase, larvicidal, reversal of TRAIL resistance and wound healing activities.

The MeOH fruit extract of *C. thevetia* exhibited cytotoxic activity against HTB-81 prostate, HTB-22 breast and HTB-38 colorectal cancer cells. Out of 33 cardenolides isolated from the seeds of *C. thevetia*, the strongest cytotoxicity against P15 lung, SW1990 pancreatic and MGC-803 gastric cancer cells was observed in peruvoside, neriifolin and ruvoside. Against Ca9-22 gingival, HSC-2 mouth and HSC-4 tongue cancer cells, the cytotoxicity of cerberin was the strongest, followed by neriifolin and thevefolin. Digitoxigenin 3-*O*-β-D-galactosyl-(1→4)-α-L-thevetoside, a new compound, was the most cytotoxic among seven cardenolides tested against P15 lung, SW1990 pancreatic and MGC-803 gastric cancer cells. Its outstanding IC_{50} values were much stronger than those of thevetioside C, which ranked second.

3.4. Toxicity

Suicidal poisoning from *C. thevetia* (yellow oleander) is common in South Asian countries such as Nepal, India and Sri Lanka. All parts of the plant contain toxic cardiac glycosides (thevetins A and B, and neriifolin) with the highest concentration in the seeds. Investigations and treatments developed for digoxin are used in the management of *C. thevetia* poisoning because of their structural similarity. Poisoning from yellow

oleander causes cardiotoxic disorders (bradycardia or irregular pulse), and gastrointestinal effects (abdominal pain, diarrhea, nausea and vomiting,). In Sri Lanka, the human mortality associated with yellow oleander poisoning has been reported to be 10%. Studies using animal models have been successfully employed to evaluate treatment protocols for management of toxic yellow oleander exposures.

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