A COMPREHENSIVE STUDY OF THEVETIA PERUVIANA: CHEMICAL PROFILE AND BIOLOGICAL ACTIVITY

Saniya[1], Mohit Saini[2], Shivani Singh[3], Rishi Gupta[4], Akash Sharma[5*]

[1,2,3,4] Research scholar, Moradabad Educational Trust Group of Institution Faculty of Pharmacy, Moradabad-244001, Uttar Pradesh, India.

[5*]Assistant Professor, Department of Pharmaceutics, Moradabad Educational Trust Group of Institution Faculty of Pharmacy, Moradabad-244001, Uttar Pradesh, India.

Corresponding Author: Akash Sharma
Email id: akashsharma3669@gmail.com

ABSTRACT

Thevetia peruviana, commonly known as yellow oleander, is a tropical ornamental plant renowned for its vibrant appearance and toxic properties. Widely distributed in India and other warm regions, it has a long-standing presence in traditional medicine despite its well-documented toxicity. This plant is a rich source of diverse phytochemicals, including cardiac glycosides, flavonoids, triterpenoids, and sterols, which contribute to its wide spectrum of biological activities. Key chemical constituents such as amyrin, β-sitosterol, cerberin, and peruvoside exhibit pharmacological properties ranging from antioxidant and antimicrobial to anticancer and anti-inflammatory effects. Notably, *T. peruviana* has also demonstrated antispermatogenic, antifertility, and anticoagulant activities, highlighting its potential in reproductive and cardiovascular research. However, the plant's toxicity, primarily due to its high content of cardenolides, presents significant challenges for therapeutic application. Ingestion of even small quantities can result in severe or fatal poisoning. Thus, safe medicinal use of *T. peruviana* necessitates rigorous extraction, purification, and toxicity testing protocols to isolate beneficial compounds while eliminating harmful constituents. Techniques such as solvent extraction and chromatography are essential to ensure standardization and safety. This review explores the botanical, chemical, and pharmacological profile of *Thevetia peruviana*, emphasizing both its medicinal potential and the critical need for caution in its application. Harnessing its therapeutic benefits while mitigating toxicity risks could open new avenues in phyto-pharmaceutical development.

Key words: *Thevetia peruviana*, Cardiac glycosides, Medicinal plants, Biological activities, Toxicity

1. INTRODUCTION

Medicinal plants comprise approximately 8000 species in India. Millions of rural households use medicinal plants in a self-help mode. Half a million practitioners of the Indian system of medicine in the oral and codified streams use medicinal plants in preventive, promotive, and curative applications. There are estimated to be over 7800 manufacturing units in India. In recent years, the growing demand for herbal products has led to a quantum jump in the volume of plant metabolites previously with unknown pharmacological activities that have been extensively investigated as a source of medicinal agents.[1,2]

Thevetia peruviana, commonly known as "yellow oleander," is a tropical plant noted for its ornamental beauty and the potent toxicity of its components. This evergreen shrub or small tree can grow up to 10 meters tall and is characterized by its elongated, glossy leaves and vibrant, funnel-shaped flowers that bloom in shades of yellow, orange, or pink. Native to parts of Southeast Asia and the Indian subcontinent, *Thevetia peruviana* thrives in warm climates and is often found in gardens and landscapes due to its attractive appearance. Belonging to the *Apocynaceae* family, this shrub is highly poisonous, with the kernels being the most toxic part. The active principles in yellow oleander are cardiac glycosides. Additionally, the physical properties of the fruit and kernel are unique and differ from those of other tree-born oilseeds, necessitating modifications in handling, storage, and transport processes associated with the fruit and kernels.[3] The extracts and preparation from the plant which are hopefully safe, exhibited various additional biological effects such as anti-oxidant, immunomodulatory, anti-cancerogenic, anti-microbial, anti-parasitic, and insect anti-fungal or repellent activities.[4]

1.1 DESCRIPTION OF PLANT

- **Name**: *Thevetia peruviana*
- **Family**: *Apocynaceae*
- **Genus**: Thevetia
- **Kingdom :** Plantae
- **Gentianales Species**: *T. peruviana*
- **Common Names**: Kolke (Bengal), Mexican oleander, Yellow Oleander, Lucky Nut
- **Taste**: Bitter
- **Colour**: Green to greenish black
- **Odour**: None
- **Shape:** Oblong, Hard

1.2 MACROSCOPIC CHARACTERISTICS

- **Growth Habit:** It is an evergreen shrub or small tree that can grow up to 10 meters tall.
- **Leaf Characteristics:** Elongated and glossy leaves, Ovate or elliptical shape
- **Flower Characteristics:** Funnel-shaped flowers
- **Vibrant Colours:** Yellow, orange, or pink
- **Fruit Characteristics:** Capsule-like structures (about 5 to 10 centimeters in length)
- **Kernel Characteristics:** Highly toxic

1.3 MICROSCOPIC CHARACTERISTICS

Leaf Structure: The leaves exhibit a well-defined cuticle and a prominent palisade mesophyll layer, which aids in photosynthesis. Stomata are typically found on the lower surface, and their density may vary based on environmental conditions.

Flower Anatomy: The funnel-shaped flowers contain numerous anthers with a rich supply of pollen, and the presence of ovules within the ovary can be noted under a microscope. The floral parts display distinct vascular bundles.

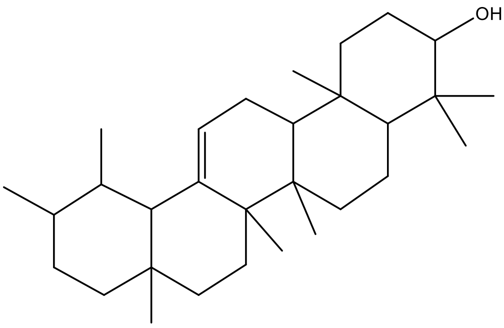
Fruit and Seed: The fruit of *Thevetia peruviana* is a follicle containing seeds that are surrounded by a hard coat. The kernel, which is the most toxic part, shows a dense cellular structure rich in cardiac glycosides.

Trichomes: The presence of glandular and non-glandular trichomes may be observed on the leaves and stems, contributing to the plant's defense mechanisms.[5]

2. CHEMICAL CONSTITUENTS

2.1 AMYRIN

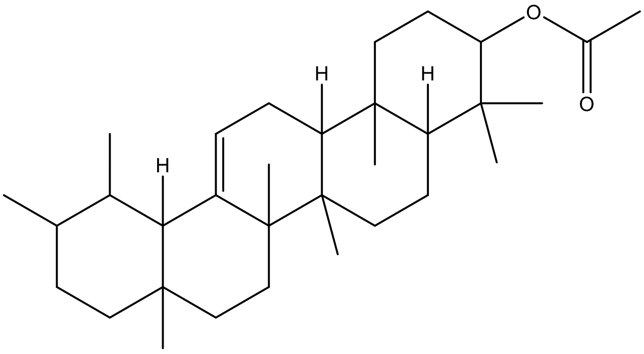
The amyrins (M1) are three closely related natural chemical compounds of the triterpene class. They are designated α-amyrin (ursane skeleton), β-amyrin (oleanane skeleton), and δ-amyrin.[6]



M1

2.2 AMYRIN ACETATE

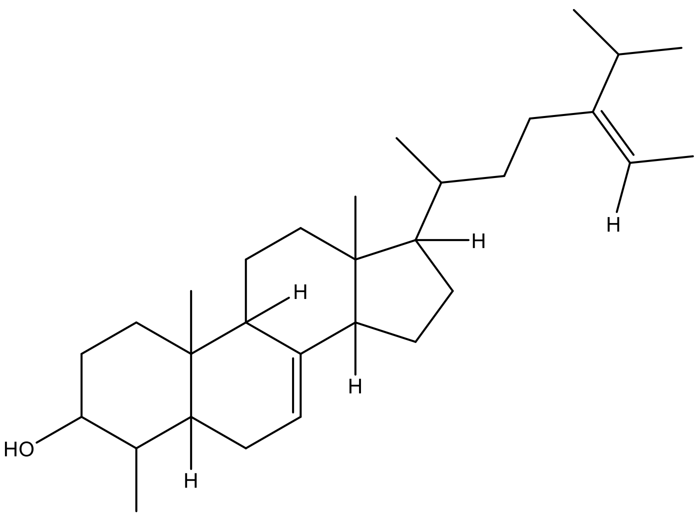
Amyrin acetate (M2) is a triterpenoid. beta-Amyrin acetate has been reported in *Erythrophleum fordii*, *Euphorbia polycaulis*, and other organisms with data available.[7]



M2

2.3 ALPHA SITOSTEROL

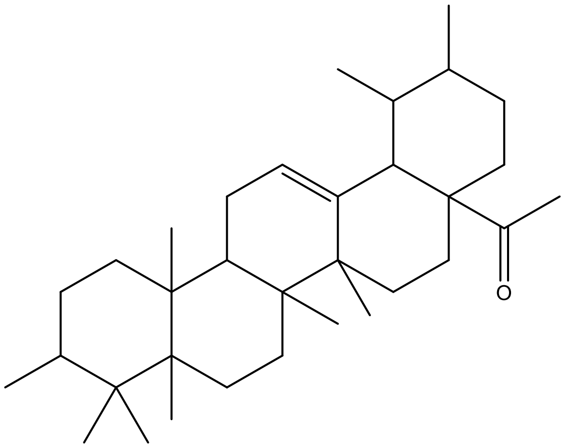
Alpha-Sitosterol (M3) has been reported in *Camellia sinensis, Neolitsea aciculata*, and other organisms with data available.[8]



M3

2.4 UROSOLIC ACID

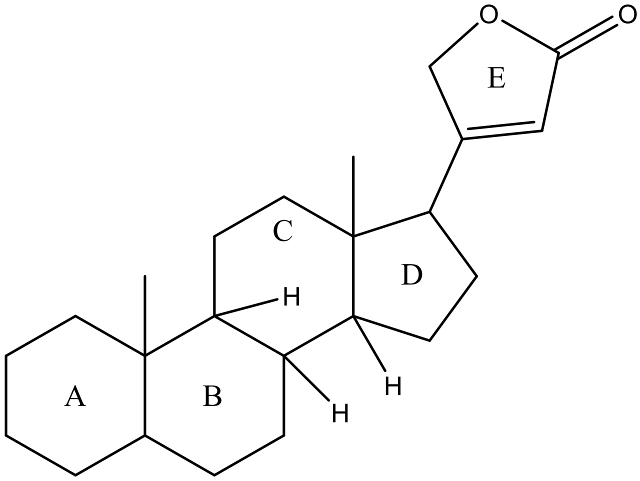
Ursolic acid (M4) (3 β-hydroxy-urs-12-en-28-oic acid) is a pentacyclic triterpenoid composed of a C-30 chemical structure built from isoprenoid units.[9]



M4

2.5 CARDENOLIDES

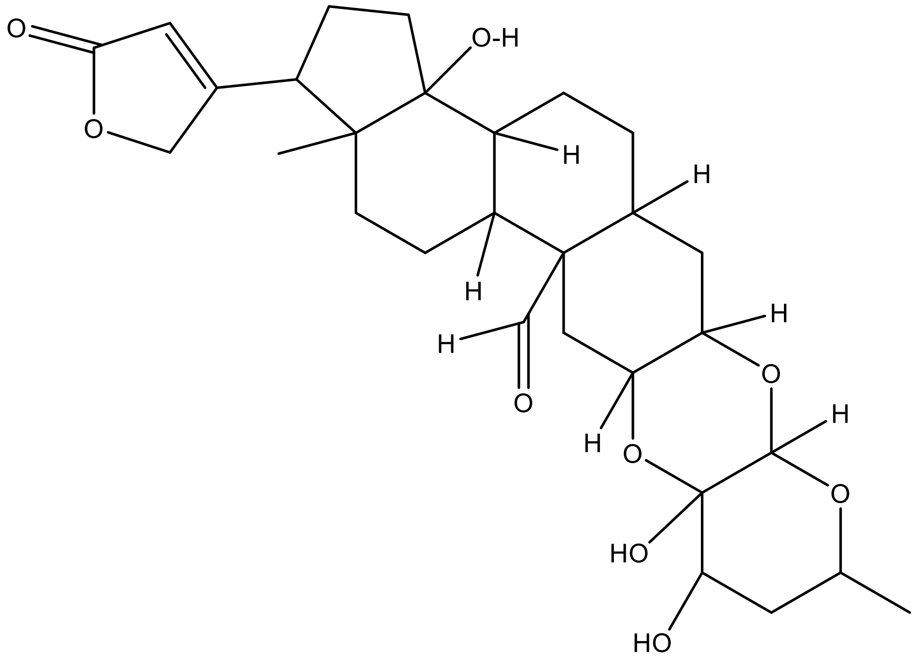
Cardenolide (M5) is a steroid with A, B, C, D and E rings lactone that is a steroid with methyl groups and a butenolide ring at 17.[10]



M5

2.6 CALOTROPIN

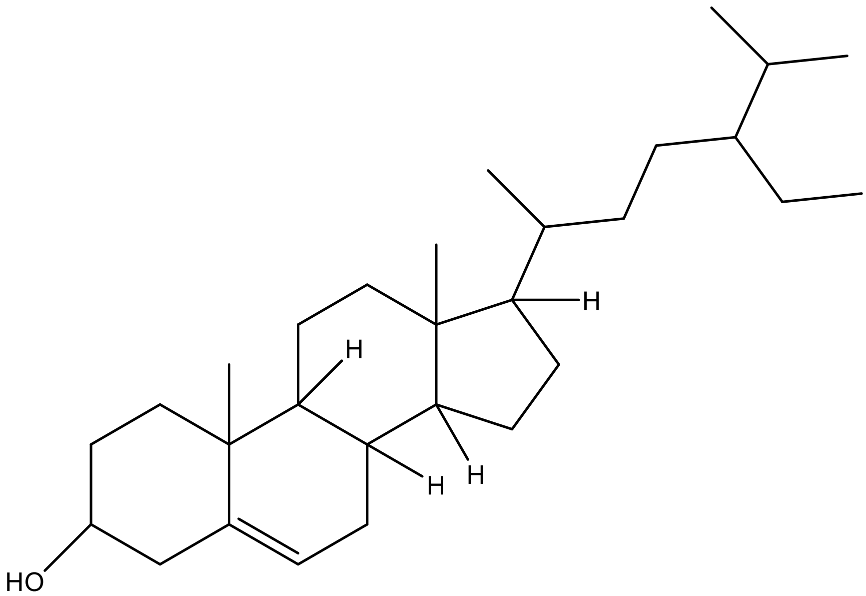
Calotropin (M6) is identified as a highly potent cardenolide that has a similar chemical structure to cardiac glycosides (such as digoxin and digitoxin).[11]



M6

2.7 BETA- SITOSTEROL

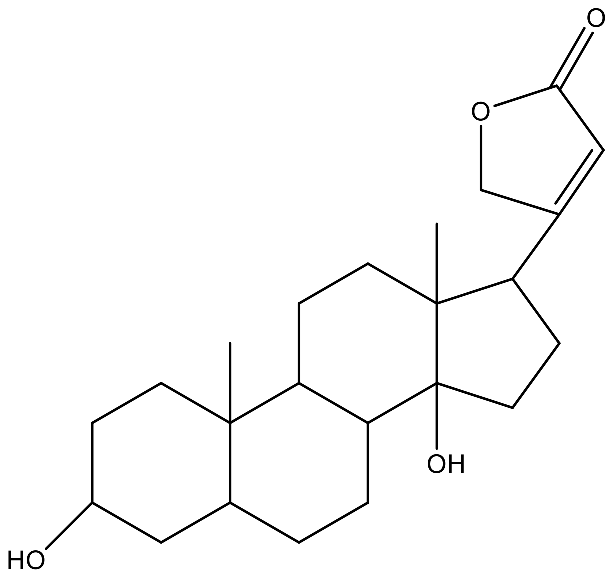
β-Sitosterol (M7) (beta-sitosterol) is one of several phytosterols (plant sterols) with chemical structures similar to that of cholesterol.[12]



M7

2.8 CARDIAC GLYCOSIDES

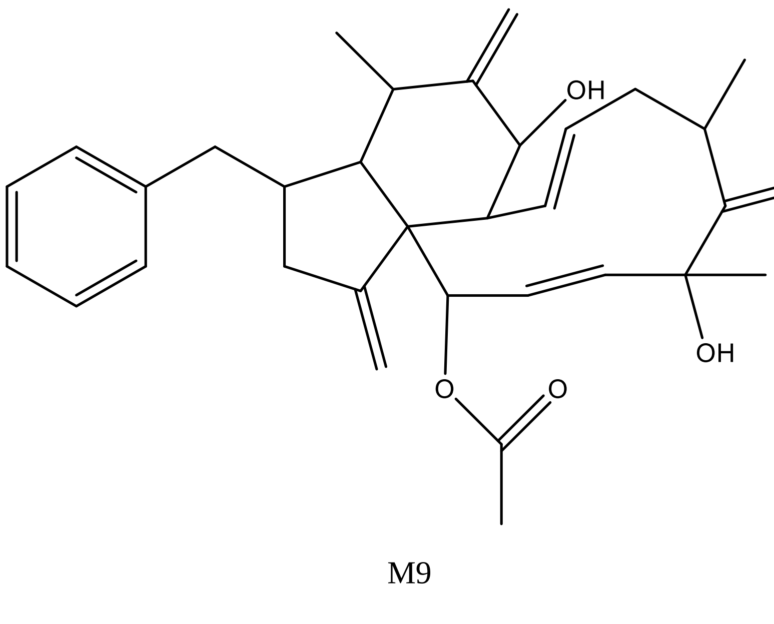
Cardiac glycosides (M8) bind and inhibit the sodium and potassium pump affecting the heart. Digoxin, ouabain, oleandrin and bufalin are the most well known cardiac glycosides.[13]



M8

2.9 CYTOCHALASIN

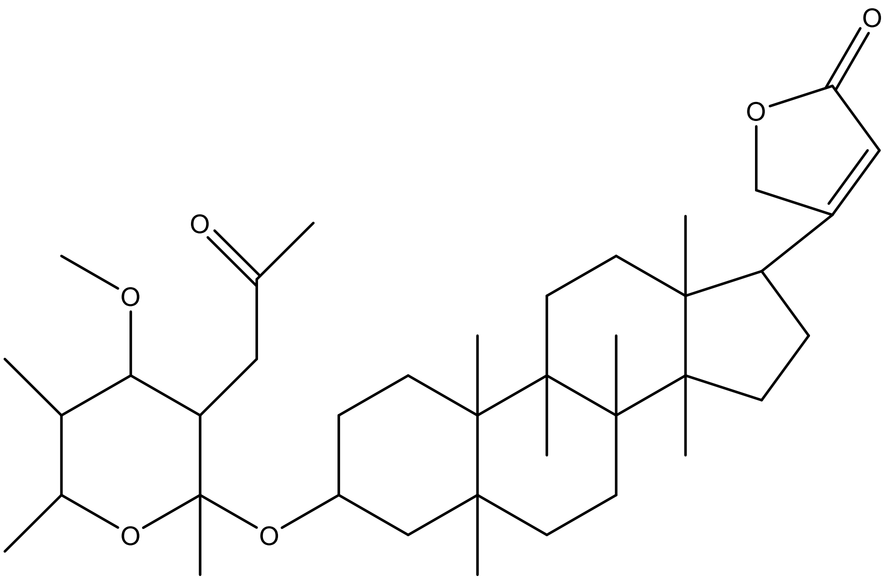
The cytochalasins (M9) are natural occurring compounds that contain an isoindolone moiety fused to a macrocyclic lactone.[14]



M9

2.10 CERBERIN

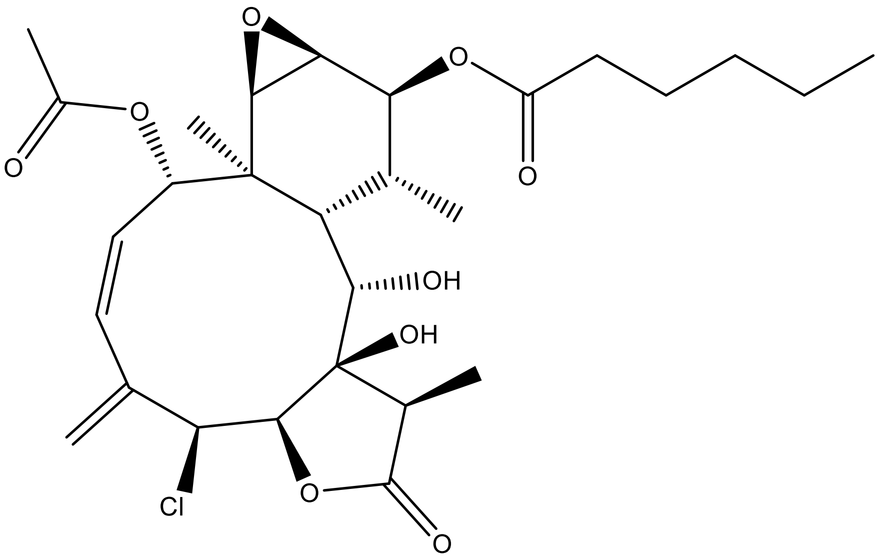
Cerberin (M10) is a cardenolide glycoside that is the 2'-acetyl derivative of neriifolin. It has a role as an antineoplastic agent and a metabolite.[15]



M10

2.11 SOLANOSIDE

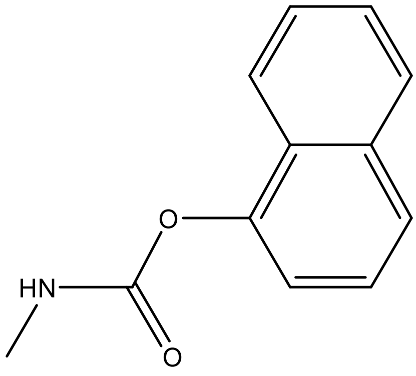
Solasodine (M11) is an oxaspiro compound and steroid alkaloid sapogenin with formula $C_{27}H_{43}NO_2$ found in the Solanum (nightshade) family. It is used as a precursor in the synthesis of complex steroidal compounds such as contraceptive pills.[16]



M11

2.12 NERIFOLLIN

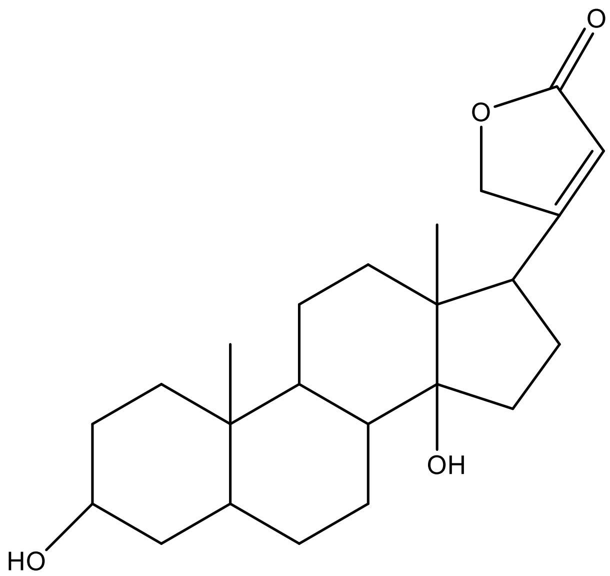
Neriifolin (M12) is a cardenolide glycoside that is digitoxigenin in which the hydroxy goup at position 3 has been converted to its (6-deoxy-3-O-methyl-alpha-L-glucopyranoside derivative.**[17]**



M12

2.13 THEVETIA FLAVONE

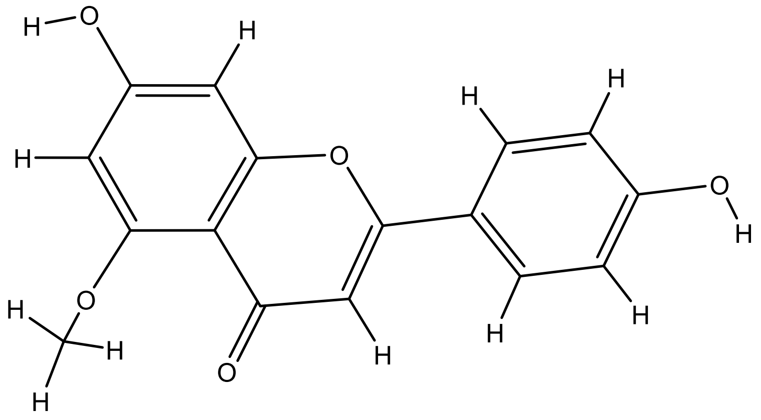
Thevetia peruviana (M13) (Pers.) K. Schum *or Cascabela peruviana* (L.) Lippold (commonly known as ayoyote, codo de fraile, lucky nut, or yellow oleander), native to Mexico and Central America, is a medicinal plant used traditionally to cure diseases like ulcers, scabies, hemorrhoids and dissolve tumors.[18]



M13

2.14 PERUVOSIDE

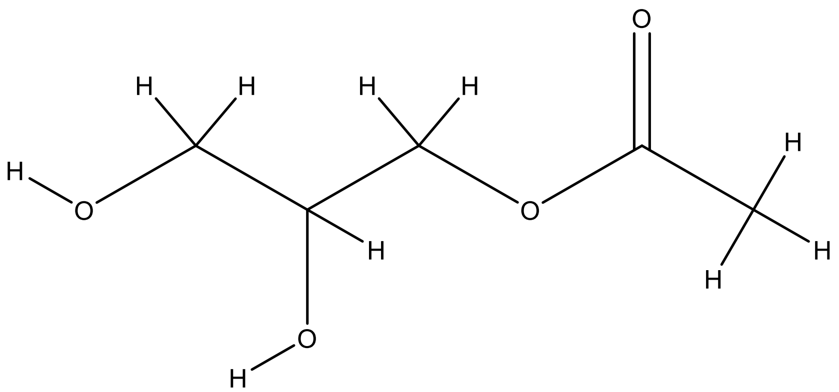
Peruvoside (M14) is a cardenolide glycoside. Peruvoside has been reported in Thevetia peruviana with data available. PERUVOSIDE is a small molecule drug and has 1 investigational indication.[19]



M14

2.15 DIHYDRONERIFOLLIN-2 ACETATE

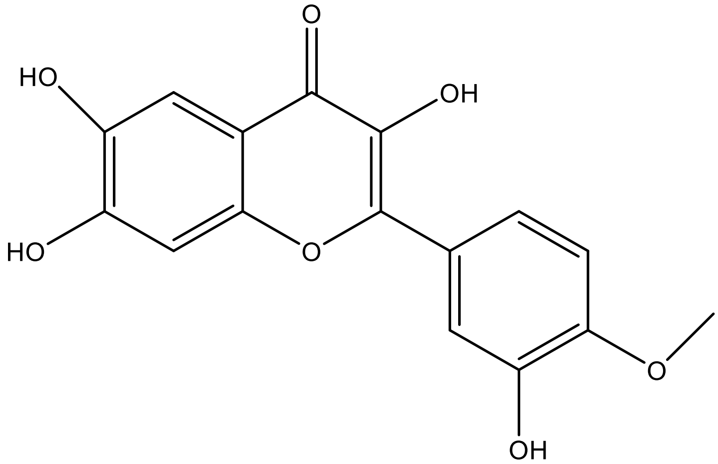
Dihydronerifollin, (M15) as a related compound, might exhibit similar toxicity. This could affect the heart by disrupting ion channels or interfering with cellular processes in cardiac tissue.[20]



M15

2.16 3,3',5,7-TETRAHYDROXY-4-METHOXYFLAVONE

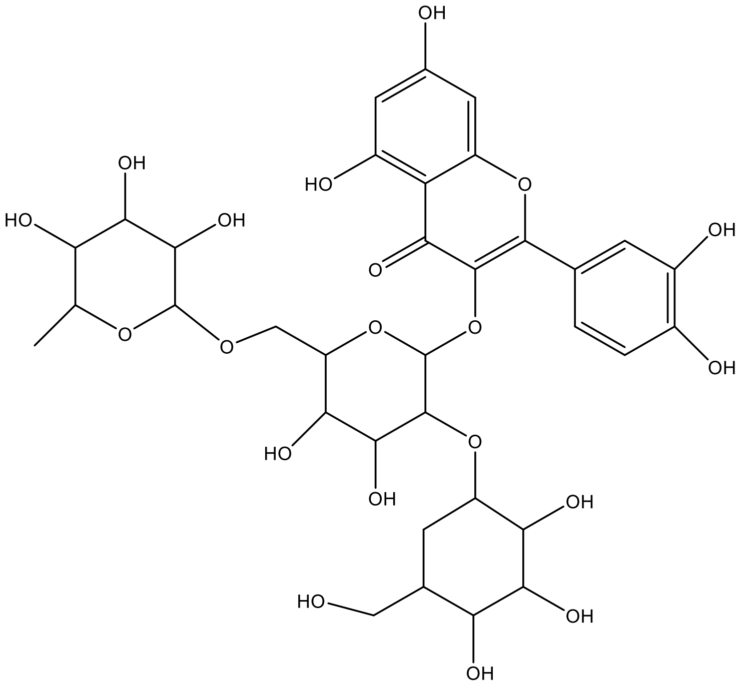
3,3',5,7-tetrahydroxy-4-methoxyflavone (M16) are well-known for their antioxidant properties, which help to neutralize free radicals and reduce oxidative stress.[21]



M16

2.17 PERUVIANOSIDE III

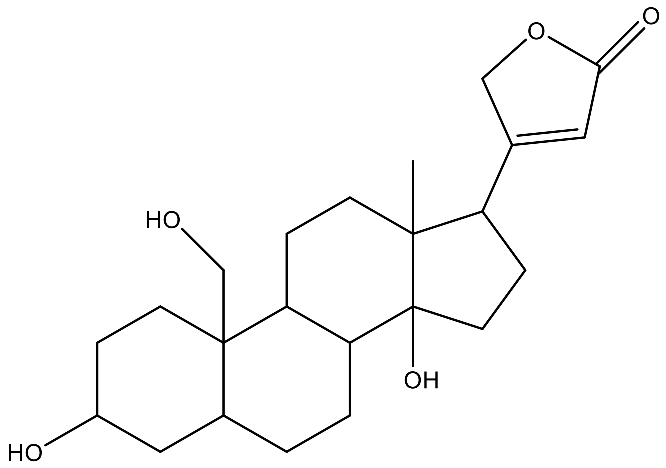
Peruvianoside III, (M17) are known for their potent effects on the heart, particularly for their ability to influence the sodium-potassium ATPase (Na^+/K^+ ATPase) pump, which plays a critical role in maintaining ion gradients across cell membranes.[22]



M17

2.18 3,14,19 TRIHYDROXYCARD-20[22]-ENOLIDE

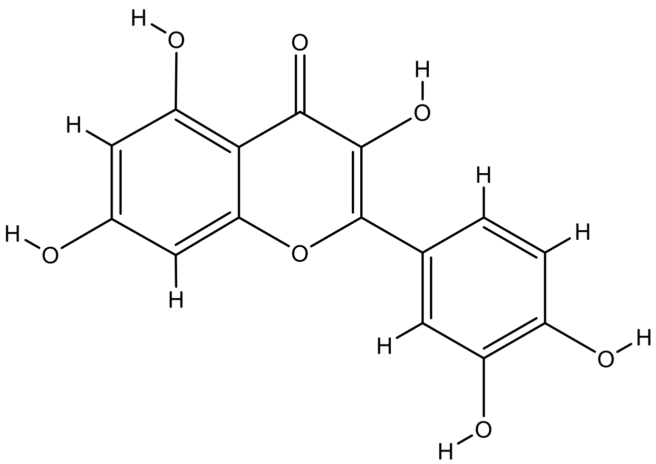
3,14,19-trihydroxycard-20[22]-enolide (M18) primarily affect the cardiovascular system by inhibiting the Na^+/K^+ ATPase pump, leading to an increase in intracellular sodium and calcium.[23]



M18

2.19 QUERCITIN

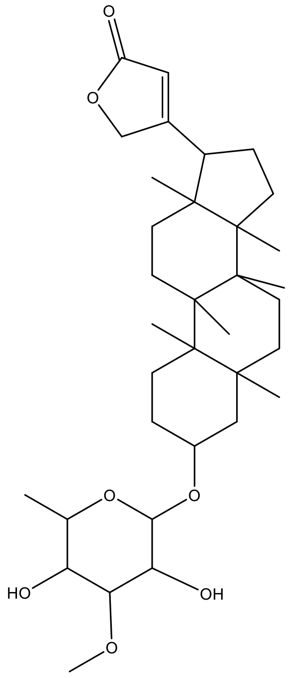
The molecule of quercetin (M19) consists of a basic flavonoid skeleton, that is, two benzene rings attached (A, B) to a heterocyclic pyrene (C), and differs from the other flavonoid compounds due to the position of five hydroxyl groups, one at position 3 of ring C, two at positions 3',4' of ring B, and another two at ring A. [24]



M19

2.20 THEVEFOLIN

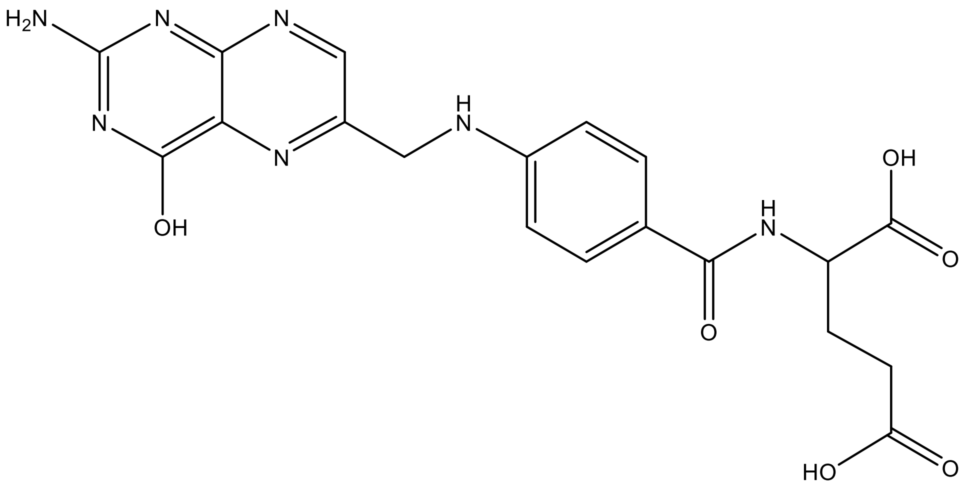
Thevefolin (M20) is likely to exhibit strong antioxidant properties. Flavonoids can scavenge free radicals and reduce oxidative stress, which helps to protect cells and tissues from damage caused by reactive oxygen species (ROS).[25]



M20

2.21 THEVEFOLIC ACID

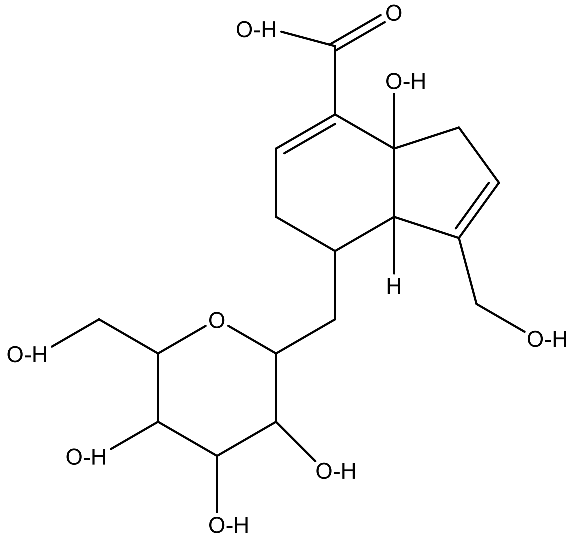
Thevefolic acid (M21) [(2S)-2-[[4-[(2-amino-4-oxo-1H-pteridine-6-yl) methylamino] benzoyl]amino] pentanedioic acid] is an odorless orange-yellow in color, with a molecular weight about 441.404 g/mol.[26]



M21

2.22 THEVESIDE

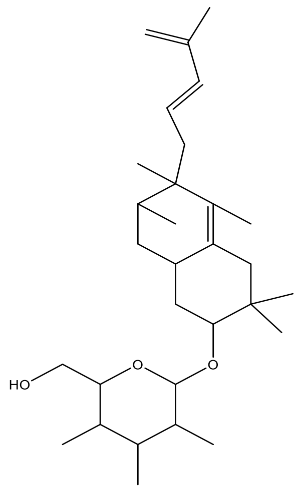
Theveside (M22) belongs to a class of compounds known as cardiac glycosides, which are known for their ability to affect the cardiovascular system. Cardiac glycosides exert their effects by inhibiting the Na^+/K^+ ATPase pump, leading to an increase in intracellular calcium levels.[27]



M22

2.23 CHEIRANTHOSIDE III

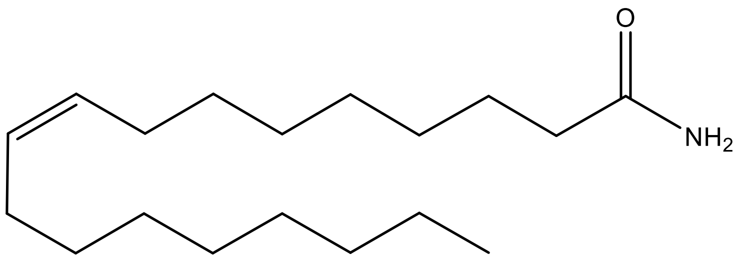
Cheiranthoside III (M23) belongs to a class of compounds known as cardiac glycosides, which are known for their ability to affect the cardiovascular system. Cardiac glycosides exert their effects by inhibiting the Na^+/K^+ ATPase pump, leading to an increase in intracellular calcium levels.[28]



M23

2.24 OLEAMIDE

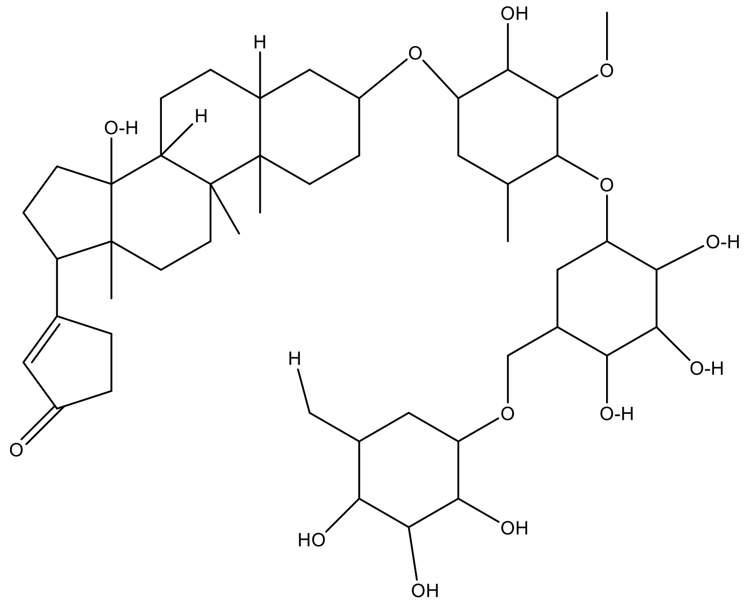
Oleamide (M24) is the amide derived from the fatty acid oleic acid. It is a colorless waxy solid and occurs in nature. Sometimes labeled as a fatty acid primary amide (FAPA), it is biosynthesized from N-oleoylglycine.[29]



M24

2.25 THEVETIN B

Thevetin B (M25) is a trisaccharide derivative and a gentiobiosylthevetoside. It is functionally related to a digitoxigenin. Thevetin B has been reported in *Thevetia ahouai*, *Thevetia peruviana*, and *Cerbera manghas* with data available.[30]



M25

Toxicity: It is important to mention that *Thevetia peruviana* is known to be highly toxic to humans and animals, primarily due to the presence of cardenolides. All parts of the plant, including its seeds and latex, contain toxic compounds that can cause severe health effects if ingested.[31]

3. BIOLOGICAL ACTIVITIES OF *THEVATIA PERUVIANA*

3.1 ANTI-SPERMATOGENIC ACTIVITY

The anti-spermatogenic activity of *Thevetia peruviana*, commonly known as yellow oleander, has been investigated for its potential effects on male fertility. Studies have shown that extracts from various parts of the plant, including the seeds and leaves, exhibit anti-spermatogenic properties, meaning they can reduce sperm production. These effects are typically attributed to the toxic compounds in the plant, such as cardiac glycosides, which interfere with spermatogenesis by affecting the endocrine system, altering hormonal levels, and impairing testicular function. Research has indicated that administration of *Thevetia peruviana* extracts in animal models leads to a decrease in sperm count, motility, and overall fertility. While these findings suggest a potential for developing male contraceptives, caution is needed due to the plant's toxicity, which can lead to severe side effects or poisoning in humans. [32]

3.2 ANTI-OXIDANT ACTIVITY

Thevetia peruviana has been studied for its antioxidant activity, which is attributed to the presence of bioactive compounds such as flavonoids, phenols, and glycosides in its various plant parts, including leaves, seeds, and flowers. These compounds have been shown to possess significant free radical scavenging abilities, which help in neutralizing harmful reactive oxygen species (ROS) in the body.[33]

3.3 ANTI-CANCER ACTIVITY

Thevetia peruviana has demonstrated potential anticancer activity in various scientific studies, primarily attributed to its bioactive compounds, such as cardiac glycosides, alkaloids, and flavonoids.

These compounds are believed to exert anticancer effects through multiple mechanisms, including inducing apoptosis (programmed cell death), inhibiting cell proliferation, and suppressing tumor growth. Research has shown that extracts from *Thevetia peruviana* can inhibit the growth of different cancer cell lines, including those related to breast, lung, and liver cancers. The plant's compounds are thought to interfere with cellular signaling pathways involved in cancer progression, including those regulating cell cycle and apoptosis. However, despite these promising results, the plant's toxicity, particularly due to its cardiac glycosides, raises concerns about its safety for use in cancer therapy. The toxic nature of *Thevetia peruviana* can lead to serious side effects, including heart arrhythmias and organ toxicity, which limits its clinical application without careful monitoring. Further research is necessary to isolate and understand the specific compounds responsible for the anticancer effects and to assess their safety and efficacy in therapeutic contexts.[34]

3.4 ANTI-COGULANT ACTIVITY

Thevetia peruviana has shown potential anticoagulant activity in various studies, which is attributed to its bioactive compounds, including cardiac glycosides and flavonoids. These compounds are believed to influence the blood coagulation pathway by modulating the activity of clotting factors and enzymes involved in hemostasis. Research has suggested that extracts of *Thevetia peruviana* can inhibit platelet aggregation and reduce blood clot formation, thus demonstrating anticoagulant properties. This could be beneficial in preventing thrombotic events such as heart attacks or strokes.[35]

3.5 ANTI-MICROBIAL ACTIVITY

Thevetia peruviana has shown promising anti-microbial properties in several studies, with various parts of the plant, including its leaves, seeds, and bark, demonstrating activity against a range of pathogens. Research indicates that extracts from *Thevetia peruviana* exhibit significant anti-microbial effects against both bacterial and fungal infections. The plant's bioactive compounds, such as cardiac glycosides, flavonoids, and alkaloids, are believed to be responsible for this anti-microbial activity. These compounds work by disrupting microbial cell walls, inhibiting enzyme activity, and interfering with the reproduction and growth of pathogens.[36]

3.6 ANTI-DIABETIC ACTIVITY

Thevetia peruviana has been investigated for its potential anti-diabetic activity, with studies suggesting that various parts of the plant, such as the leaves and seeds, may have a beneficial impact on blood sugar regulation. The plant contains bioactive compounds, including alkaloids, flavonoids, and glycosides, which are believed to play a role in improving insulin sensitivity and modulating glucose metabolism. Research on animal models has indicated that *Thevetia peruviana* extracts can help lower blood glucose levels, potentially through mechanisms such as enhancing insulin secretion or inhibiting enzymes involved in carbohydrate digestion and absorption. These effects may contribute to better blood sugar control in diabetic conditions.[37]

3.7 ANTI-FERTILITY ACTIVITY

Thevetia peruviana has demonstrated anti-fertility activity in various studies, particularly due to the presence of toxic compounds like cardiac glycosides. Research suggests that extracts from the plant, especially from the seeds and leaves, can impair fertility in both male and female animals. In males, *Thevetia peruviana* has been shown to reduce sperm count, motility, and overall fertility by affecting the endocrine system, disrupting hormonal balance, and interfering with spermatogenesis. In females, the plant's extracts may influence hormonal regulation and ovarian function, potentially leading to a decrease in fertility.[38]

3.8 ANTI-FUNGAL ACTIVITY

Thevetia peruviana has demonstrated notable antifungal activity, with various studies highlighting its potential in combating fungal infections. The plant contains bioactive compounds such as cardiac glycosides, flavonoids, and alkaloids, which have been found to exhibit significant anti-fungal properties. Research has shown that extracts from different parts of the plant, including the seeds, leaves, and flowers, possess inhibitory effects against a range of fungal pathogens, including *Candida albicans*, *Aspergillus niger*, and *Trichophyton* species. These compounds are believed to work by disrupting the fungal cell membrane, inhibiting enzyme activity, and interfering with the growth and reproduction of the fungi. The antifungal activity of *Thevetia peruviana* suggests its potential as a natural treatment for fungal infections, especially those resistant to conventional anti-fungal agents. However, the plant’s toxicity, particularly from the cardiac glycosides, raises concerns regarding its safe use in clinical applications. As a result, further research is needed to isolate and understand the specific compounds responsible for the anti-fungal effects and to assess their safety and therapeutic potential.[39]

3.9 ANTI-INFLAMMATION ACTIVITY

Thevetia peruviana, commonly known as the yellow oleander, has garnered attention for its potential anti-inflammatory properties. Various studies have indicated that extracts from the plant may inhibit the production of pro-inflammatory cytokines, thereby reducing inflammation in various tissues. The phytochemical components found in *Thevetia peruviana*, such as flavonoids and alkaloids, are thought to modulate inflammatory pathways, offering therapeutic benefits in conditions characterized by chronic inflammation. Additionally, traditional medicine practices have utilized this plant for its purported anti-inflammatory effects, further emphasizing its relevance in natural health remedies. However, it is essential to approach the use of Thevetia peruviana with caution, as parts of the plant can be toxic, necessitating careful dosage and further scientific investigation to fully understand its efficacy and safety in anti-inflammatory applications.[40]

CONCLUSION

Thevetia peruviana, is a plant that contains a wide range of active compounds, including amyrin, amyrin acetate, beta-sitosterol, nerifollin, quercetin, and calotropin, which have shown promising therapeutic properties in various scientific studies. These compounds are associated with beneficial biological activities such as spermatogenic effects, antidiabetic properties, anti-inflammatory effects, and potential anticancer activity. Despite these promising uses, the plant also contains several toxic compounds, including thevetin B, cerberin, nerifollin, and peruvoside, which are highly toxic and can lead to serious health risks such as poisoning or even death if not handled properly. The presence of these harmful substances underscores the need for careful preparation and use of *Thevetia peruviana* in medicinal applications. To safely harness its medicinal properties, it is critical to establish precise dosages and administer the plant's extracts under controlled conditions. The therapeutic formulations must be rigorously standardized to ensure the correct concentrations of non-toxic, bioactive compounds, while minimizing or eliminating the presence of toxic ingredients. Additionally, each stage of preparation should involve comprehensive toxicity testing to confirm the safety and effectiveness of the final product. The purification process should aim to separate and isolate the beneficial compounds from the toxic ones, employing techniques such as solvent extraction, chromatography, and crystallization. All these processes should be conducted under strict supervision by trained professionals to ensure that only safe, non-toxic components are used for therapeutic purposes. By adhering to these precautions, it is possible to safely integrate *Thevetia peruviana* into medicinal applications while minimizing the risks of toxicity and maximizing its potential health benefits.

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