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Review Article

Thevetia peruviana: अश्वाघना: the Good Luck tree

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Abstract

This paper studied *Thevetia peruviana,* of the family Apocynaecae a plant that is native of North America and Mexico, that has been used as an anti-inflammatory, anti-microbial, and an anti-oxidant. The paper has made an attempt in presenting a comprehensive review of the six decades of extensive research conducted on this plant; with respect to its medicinal significance. A comprehensive account of its chemical constituents and the pharmacological activities are presented in this paper, in view of the many recent findings of importance with regards to this plant. A wide range of secondary metabolites such as Enolides, Flavones; Thevetoside; Theveside; Glycosides; and Flavanones have been isolated from this plant, exhibiting diverse and extreme array of biological activities. Extracts from seeds, flowers, leaves, and bark of this plant, possess useful pharmacological activities. In conclusion, it is inferred that Thevetia *peruviana* is a well studied plant of medicinal value. It has scientifically proven to show anti-microbial activity from the oil of the plant that contains flavonoids; anti-inflammatory activity from the extracts of the flowers that contain quercetin, kaempferol and quercetin-7-O-galactoside; strong immunomodulatory activity due to Kaempferol; β-sisterol present in the bark of the plant shows presence of anti-fungal and anti-bacterial activity and thevefolin isolated from seeds showed anti-cancer activity and cardiotonic activity.

Keywords: *Thevetia peruviana,* chemical constituents and pharmacological review

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1. Introduction

Thevetia peruviana, (pers) K Shum belongs to the family Apocynaceae, is a native of North America, and Mexico and is being cultivated in South East Asia. The other botanical synonyms of this plant are *Thevetia neriifolia Juss*, and Cerbera Thevetia *Leeds.* It grows as a shrub or tree no taller than 8 m tall. The flora consists of yellow tubular flowers consisting of five petals that are faintly fragrant, spirally arranged leaves, glabrous branchlets exuding white toxic latex and a yellowish green fruit that is a laterally compressed drupe with mericarps united into an obdeltoid shape.

Thevetia peruviana, is also commonly known[3, 30] in different countries by locals as Good Luck Tree; Be Still Tree; Digoxin; Lucky Nut (Virgin Islands); Nerium Oleander; Yellow Oleander (United States); Cabalonga; caballón (Puerto Rico, Spanish); retama (Dominican Republic); chirca, campanilla (Mexico); chilca (Central America); chilindrón; campanilla amarilla (El Salvador); cobalonga(Puerto Rico, Spanish), cachimolivo, jorro jorro; azuceno, cascavel, castañeto, amancay (Columbia); manzanillo, retama (Venezuela); zuche, jacapa (Ecuador); ahouay, llagas de San Francisco (Argentina); trumpet-flower, luck-seed (United

States); lucky bean bush; noho-malie (Hawaii) ; bois saisissement, serpent, d'eau livre (Haiti) ; joro-joro, and olijfi di Bonaire (Encyclopaedia of World of Medicinal Plants).

The Sanskrit names for *Thevetia peruviana*, found in the encyclopaedia of medicinal plants are Ashvaghna (अश्वाघना), Divyapusha (दिव्यपूषा), and Haripriya (हरिप्रिया) [30] (Encyclopaedia of World of Medicinal Plants). The medicinal value of this plant ranges from the being an extreme cardiotonic agent [34], antineoplastic agent [11], cardioactive glycoside [18], feeding deterrent, showing cytotoxic as well as antimicro bacterial properties [6], antifungal [8], anti-diarrhoeal; HIV-1 reverse transcriptase and HIV-1 integerase inhibitory agents [16].

There are 8 species for the genus *Thevetia*, most of which originates in the tropical America. *Thevetia peruviana* is the only species that is cultivated in South-East Asia [15]. This genus is named after the French missionary and explorer Andre Thevet (1502–1590) who described the flora and fauna native on the Bay of Rio de Janerio and was the first one to import this plant to Europe in 1556 [1]. [Fig, 01]

In conclusion, it can be inferred that Thevetia *peruviana* is a well studied plant of medicinal value. It has been scientifically studied to show anti-microbial activity from the oil of the plant that contains flavonoids; anti-inflammatory activity from the extracts of the flowers that contain flavanones; strong immunomodulatory activity due to Kaempferol- another flavonoid present in plant that is known to be a strong antioxidant; β-sisterol present in the bark of the plant showing presence of anti-fungal and anti-bacterial activity and thevefolin isolated from seeds showing anti-cancer and cardiotonic activity, that induced DR5 expression at both the mRNA and protein level, and real-time PCR study showed that thevefolin enhanced mRNA expression of DR4 and DR5 in AGS cells.

Ethnobiomedicinal origin

Thevetia peruviana has been extensively used in traditional medicine in Central, South America and South-East Asia [23]. Healers from Northern Peru from mestizo community have been using "*Maichil*" indigenous name for *Thevetia peruviana* to heal different diseases that can be traced back to Moche culture (AD 100-800) [2]. "Representations of these plants were frequently found on Moche ceramics, and the remains of some were found in a variety of burials of high-ranking individuals of the Moche elite." The origin of the name of this plant is found in Mochica community of Peru [23].

In Philippines, mixture prepared from the bark or leaves of *Thevetia peruviana* is applied in regulated doses to loosen the bowels, as an emetic, and is said to be an effective cure for intermittent fevers [16]. In Vietnam, purified thevetin is used as a cardiotonic. In Thailand and India, the oil from the kernel is applied topically to treat skin burns. In Indonesia locals use seeds are used as a purgative in rheumatism and dropsy and sometimes an ingredient of suppositories to alleviate haemorrhoids. The roots are applied as plaster to heal tumours [3].

Pharmacognosy review

Medicinal plants and their endophytes are important resources for discovery of natural products [4]. In past six decades extensive work has been done on Thevetia peruviana. French Scientist Frerejacque, Marcel was the first scientist that discovered Thevetin, Thevefolin- a cardiac glycoside from Thevetia peruviana seeds, Neriifolin, and Monoacetylneriifolin from this plant in 1947**.**

The pharmacognosy and pharmacology studies on *Thevetia neriifolia* were first conducted by the Scientist Dr. Casamada, Ramon San Martin; Real Academia Nacional de Farmacia in 1948, who used Keller-Killiani and Baljet color tests, followed by using the "foaming index" of leaf infusions in-situ, in the hearts of the frogs; discovering for the first time the toxic nature of the cardiac glycosides.

The cardiotoxic effects of Thevetia peruviana where discovered by a Chinese Scientist Li in 1962, after conducting pharmacology studies on its flowers. This discovery was followed by pharmacology studies on its folia first conducted by the Chinese as well as the Russian Scientist Aleshkina A and Berezhinskaia V, both in 1962. This was confirmed by the toxicological studies of thevetin isolated from the kernels of the Thevetia peruviana conducted in-vivo on a cat by Chinese Scientist Huang, Ching-Chang and et al; in 1964.

Thevetia peruviana plant has undergone several pre-clinical in-vitro studies, following are the notable findings from various bioactivities:

1. Anti-microbial activity

The antimicrobial activities were reported of methanol and chloroform extract of oil from the plant Thevetia peruviana; investigated against Staphylococcus aureaus, Streptococcus pyogenes, Corynebacterium ulcerans and Bacillus subtilis Gram positive. The Gram negative microbes studied for this study were Escherichia coli, Neisseria gonorrhoae, Klebsiella pneumonia, Salmonella typhiand and Shigella dysenteriaea.

It was reported that the methanol extract exhibited high activity against all the organisms tested except Klebsiella pneumoniae. The chloroform extract inhibited only two organism, Salmonella typhi and Shigella dysenteriae [17].

2. Anti-Cancer activity

“Researcher Ishibashi, conducted a screening program targeting TRAIL resistance-overcoming activity against human gastric adenocarcinoma (AGS) cells using thevefolin isolated from Thevetia peruviana, that induced DR5 expression at both the mRNA and protein level, and real-time PCR study showed that thevefolin enhanced mRNA expression of DR4 and DR5 in AGS cells, suggesting that up-regulation of death-receptor expression may be related to TRAIL resistance-overcoming activity of thevefolin” [5]. The activity of extracts from Thevetia peruviana in inhibiting cell replication capacity is analyzed. The test of cytotoxicity showed inhibition of cell replication in the three tumor cells, more effectively in the type HL-60, showing a dose-dependent correlation with major action in the concn. of 200 µg/mL. In HEP-G2 and in PC-12, the dose-dependence correlation was not observed but obtained significant inhibitions [6].

3. Anti-fungal, and anti-bacterial activity:

B-sitosterol present in Thevetia peruviana prevents the oxidation of LDL cholesterol thereby reducing the risk of atherosclerosis [35]. It has antifungal, antibacterial and anti–inflammatory activities and is also used to treat asthma, arthritis, allergies and cancer [7].

4. Antioxidant activity

Flavonoids are potent antioxidants, free radical scavengers, and metal chelators and lipid per oxidation inhibitor [5]. Quercetin – a flavonoid is a powerful antioxidant, natural anti-histamine, and anti-inflammatory found in Thevetia peruviana. Research shows that quercetin may help to prevent cancer, especially prostate cancer [36].

5. Immunomodulatory activity:

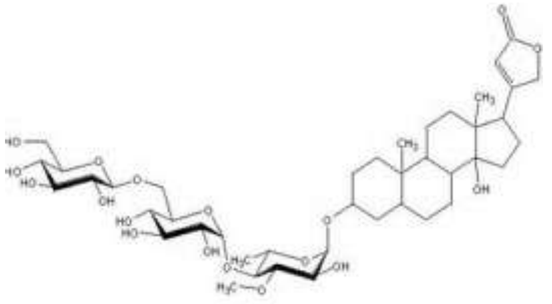
Kaempferol - another flavonoid present in Thevetia peruviana is known to be a strong antioxidant and helping to prevent oxidative damage of our cells [7] Many glycosides of kaempferol, such as kaemferitrin and astragalin, also have medicinal value.

6. Anti-inflammatory activity

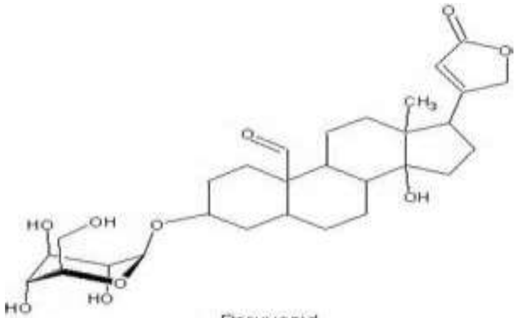
Researcher Thilagavathi, R. showed that the extracts of the flowers contain quercetin, kaempferol and quercetin-7-O-galactoside [8]. The structure of these isolated compounds were elucidated by UV, ^{1}H NMR and ^{13}C NMR spectra. The anti-inflammatory characters of these isolated compounds were tested by these researchers by vitro method, which indicated biphasic properties for these constituents.

Chemical constituents

Since 1960s, extensive studies have been conducted on the plants roots, bark, leaves, flowers, and seeds. Thevetia peruviana is widely known for its two most important cardiac active compounds, thevetin and peruvosid. Peruvosid, a cardiac glycoside has been introduced in German market as “Endocardin”[34]. Thevetin gives rise to digitalis like action on heart, making it clinical important constituent.



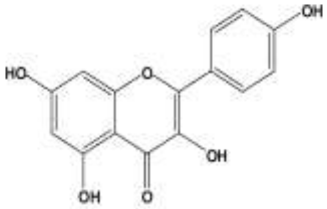
Thevetin B



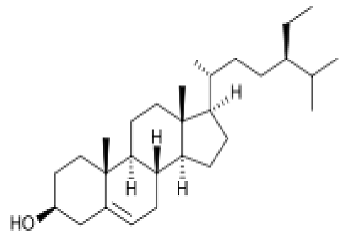
Peruvosid

Apart from these 2 compounds, researchers have isolated a total of 77 constituents from the plant species Thevetia, out of which 34 constituents are from genus peruviana. Researchers have categorized these constituents into following categories: 5 Enolides molecules; 1 Flavone molecule;1 Thevetoside molecule; 6 Theveside molecules; 1 Pentanediol molecule; 1 Pentanol molecule; 2 Pentanetriol molecules; 3 Kaempferol-3-glycoside molecules; 1 Lupen-3-ol molecule;

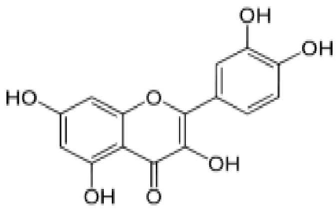
1 Lupen dien-3-ol molecule; 2 Flavanone molecules; 4 Quercetin-3-glycoside molecules; 4 Ursadien-3-ol molecules; and 1 Pentanetetrol molecule.



Kaempferol



β-Sitosterol



Quercetin

Constituents of Leaf extract of the plant:

Leaf extracts studied consisted of cardiac glycosides, sterols, iridoid glucosides, pentayclic triterpenes and a cardenolide. 7 known compounds that are known from fresh uncrushed leaves they are, 1) neolupenyl acetate, 2) 11-oxo-urs-12-en-28-oic acid, 3) lupeol acetate, 4) oleanolic acid, 5) ursolic acid, 6) stigmast-5-en-7-one, and 7) β-sitosterol.

Constituents of Seed extract of the plant:

Seeds extract's studied consisted of cardenolide triglycosides of neriifolin, acetylneriifolin and thevetin.

Constituents of Flower extract of the plant:

Its flowers showed presence of quercetin, kaempferol and quercetin-7-o-galactoside.

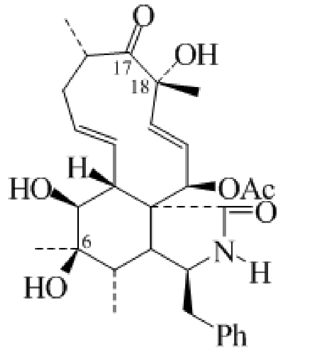
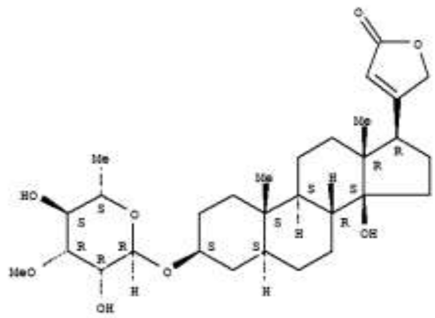
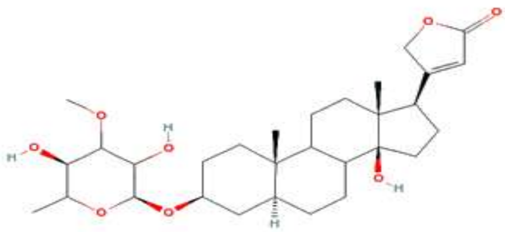
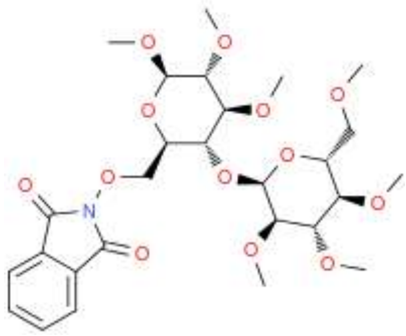
Constituents of the Bark extract of the plant:

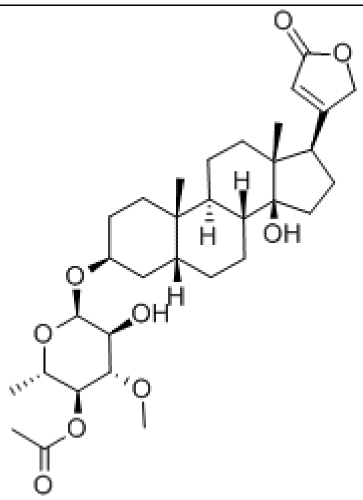
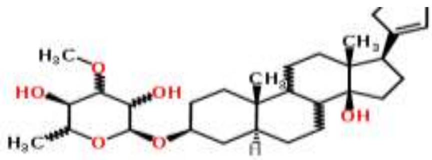
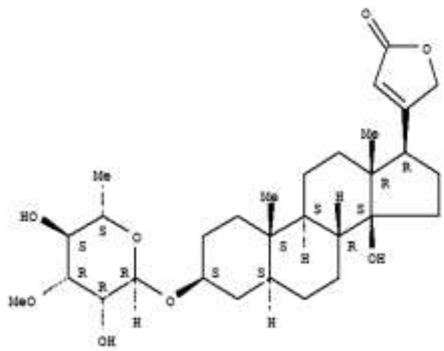
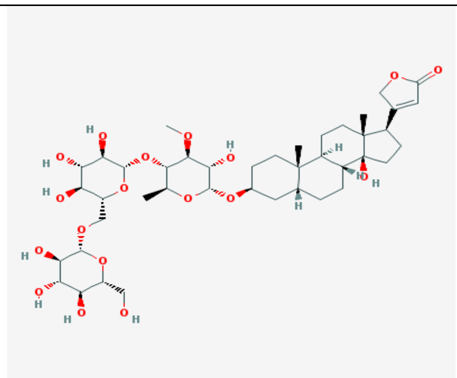
Bark extract showed presence of four cardenolide glycosides; neriifolin, thevefolin, peruvoside, and (20S)– 18, 20-epoxydigitoxigenin α-L-thevetoside.

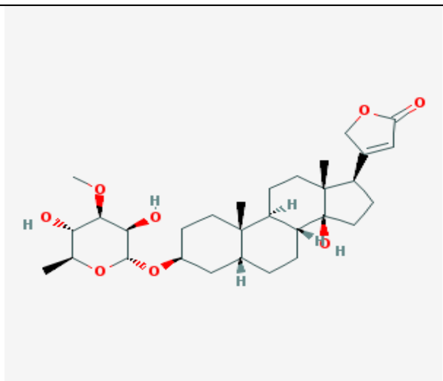
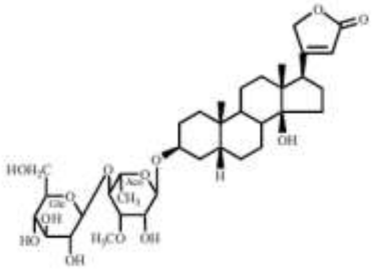
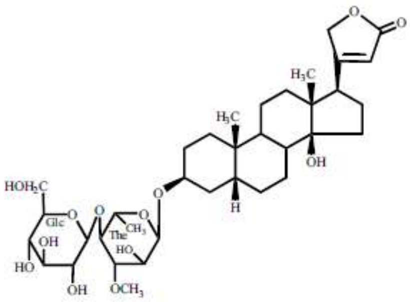
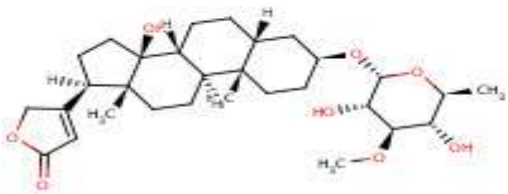
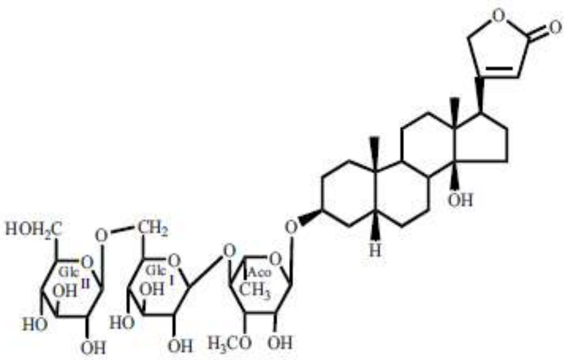
Constituents of the Root extract of the plant:

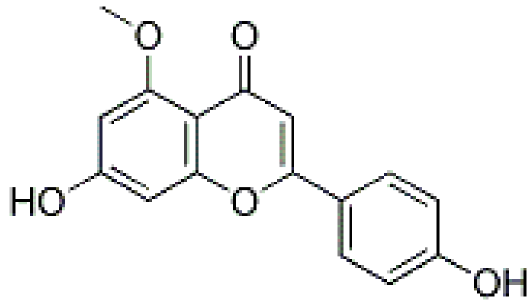
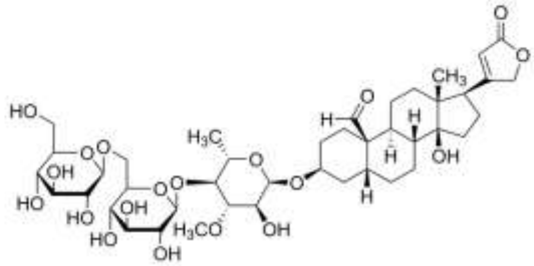
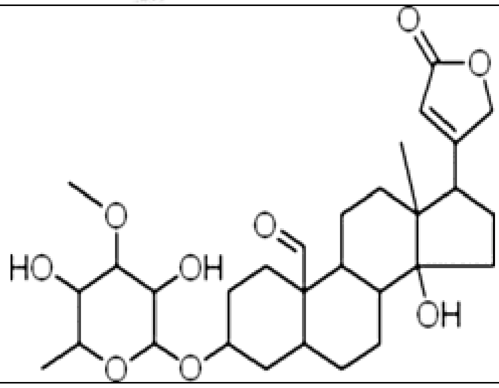
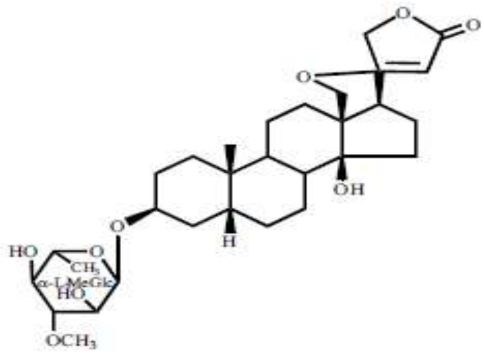
Root extract showed presence of iridoids, theveside, theviridoside, and two new glucosides theviridoside identified by Chinese researchers namely 10-O-β- D-Glucopyranosyl theviridoside and 3-O-β-D-Glucopyranosyl theviridoside.

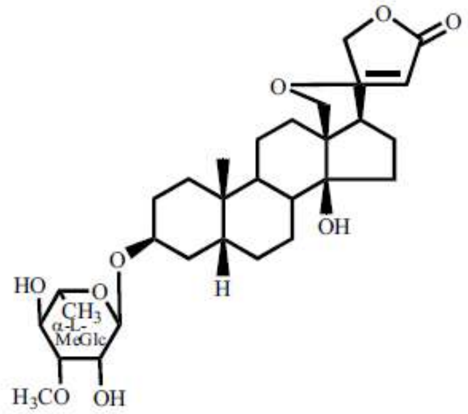
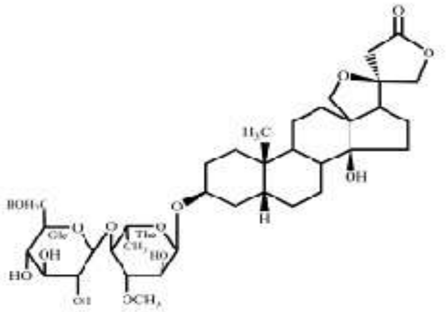
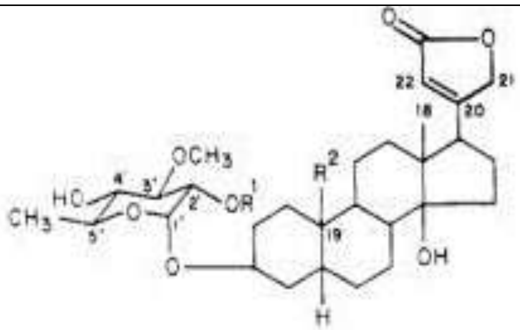
Seventy Seven "known constituents" of genus Thevetia present in Dictionary of Natural Products:

Name (IUPAC)	**Structure, Chemical name**
Cytochalasin Ohyp	 Absolute Configuration Cytochalasin Ohyp
	 Neriifoside M.F: 534.319
	 Thevefolin, M.F: 534.319
3,14-Dihydroxycard-20(22)-Enolide; (3Î²,5Î±,14Î²,17Î²)-Form, 3-O-[Î²-D-Glucopyranosyl-(1->4)-6-Deoxy-3-O-Methyl-Î±-L-Glucopyranoside] : Thevetin	 methyl 2,3,4,6-tetra-O-methyl-Î±-D-glucopyranosyl-(1->4)-2,3-di-O-methyl-6-O-phthalimido-Î²-D-glucopyranoside

Cerberin : 25633-33-4	
Thevetia Neriifolia Saponin: *144300-22-1*	
Thevetia Neriifolia Saponin 5; 144300-21-0	
Hevetia Neriifolia Saponin 3: 144300-20-9	
3,14-Dihydroxycard-20(22)-Enolide; (3Î²,5Î±,14Î²,17Î²)-Form, 3-O-(6-Deoxy-3-O-Methyl-Î±-L-Glucopyranoside) ; 34302-25-5	
145921-45-5 *Neriifoside*	
27127-79-3 : Thevetin B	

4356-33-6 : Solanoside	
197631-21-3 : Thevetia Ahouai Saponin 3	
114586-47-9 : Thevetia Nerifolia Saponin 1	
466-07-9 : Neriifolin	
141435-04-3 : Thevetia Nerifolia Saponin 2	
25633-36-7 ;	

29376-68-9 : Thevetiaflavone	
37933-66-7: Thevetin A	
1182-87-2 : Peruvoside	
71129-71-0 : Thevetia Nerifolia Saponin 6	

71183-77-2 : 18,20-Oxido-20,22-Dihydroneriifolin 2'–Acetate	
144223-74-5 : Thevetia nerifolia saponins 8	
71183-76-1 : Thevetia Nerifolia Saponin 7 (20S) 18, 20-Oxido-20,22, Dihydronerifolin	
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74048-34-3	

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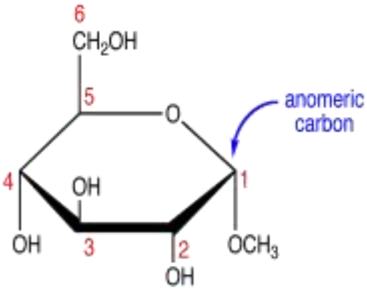
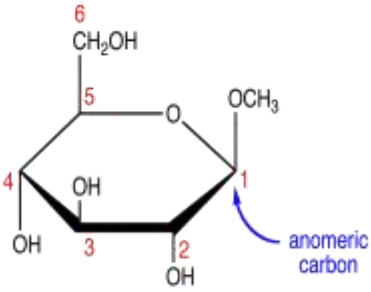
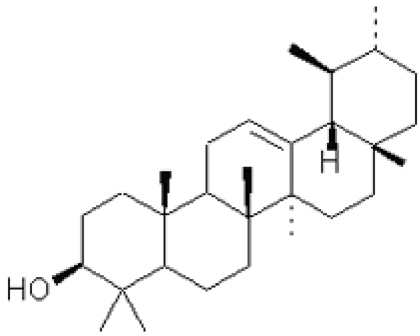


methyl α-D-glucopyranoside



methyl β-D-glucopyranoside



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3,4-Epoxy-3-(1-hydroxy-1-methylethyl)-1-pentanol; 1-O-[Î²-D-Apiofuranosyl-(1->6)-Î²-D-glucopyranoside]</td>
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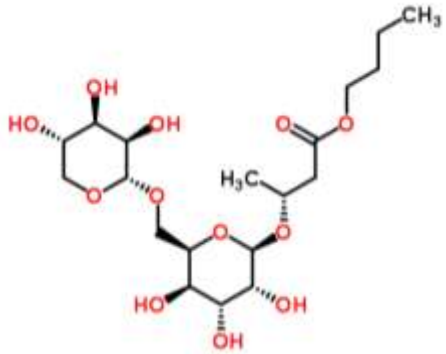

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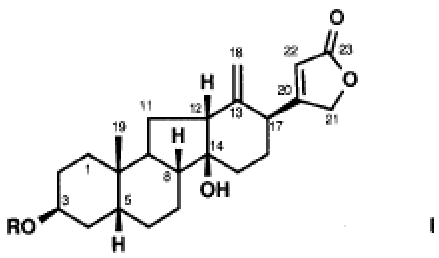

1 : R=a-1   4 : R=a-2   7 : R=a-3
2 : R=b-1   5 : R=b-2   8 : R=b-3
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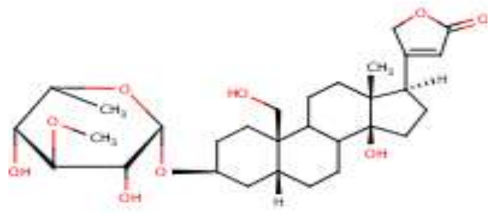
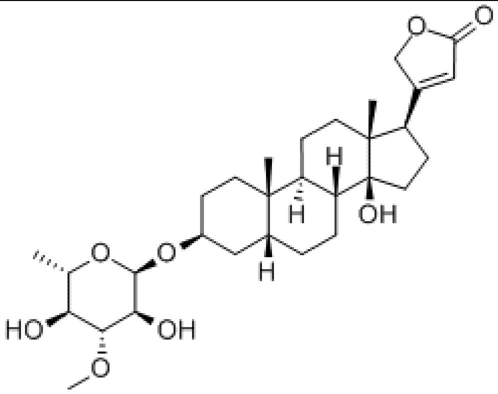
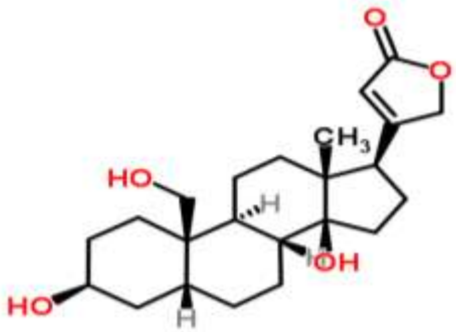
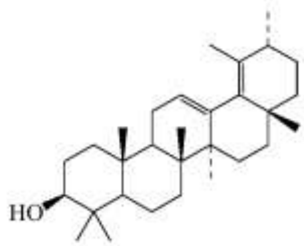
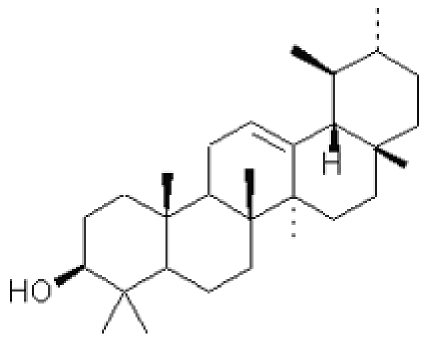
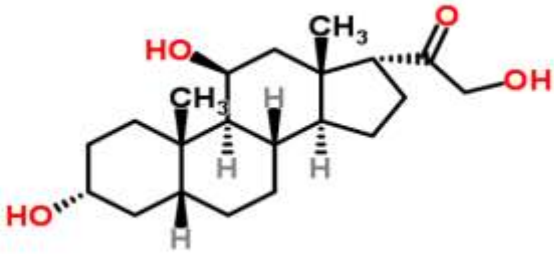
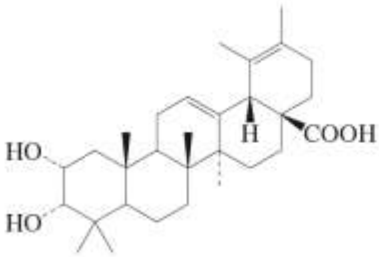
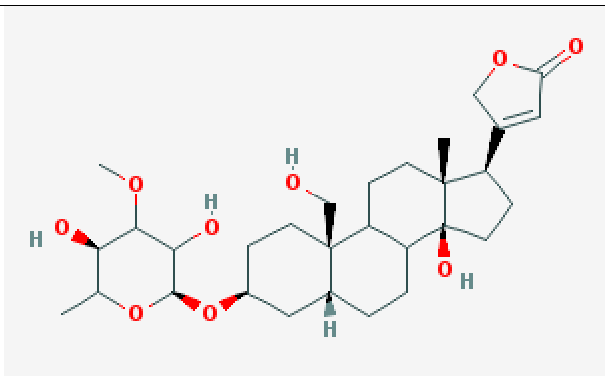
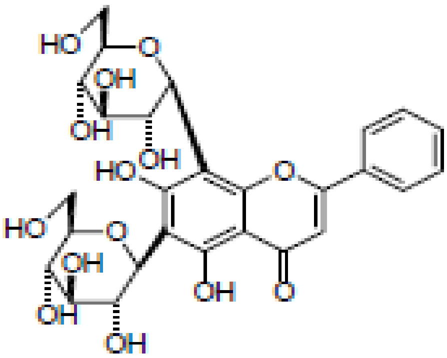
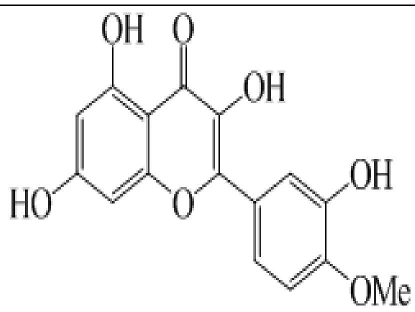
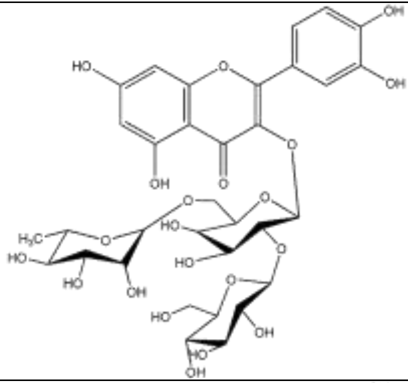
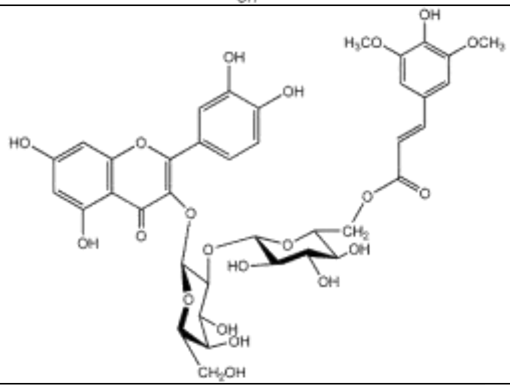
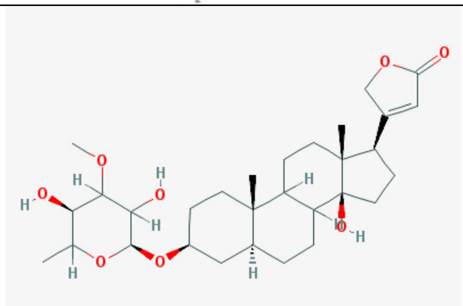
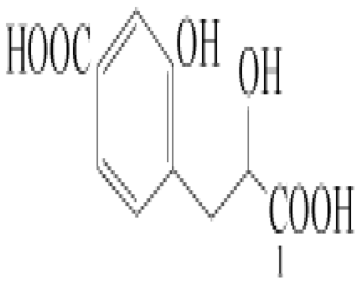
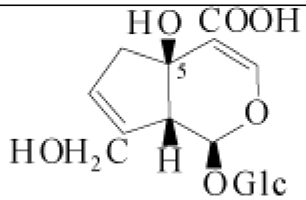
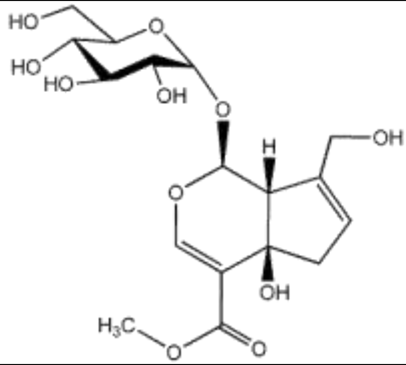
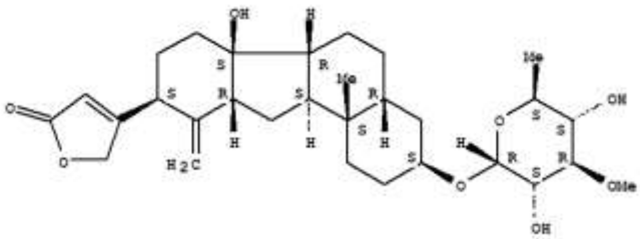
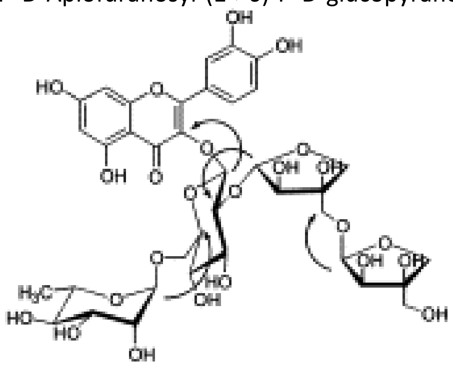
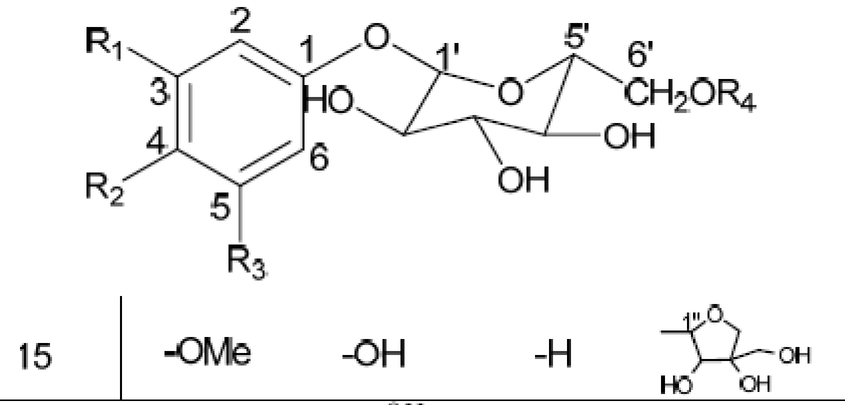
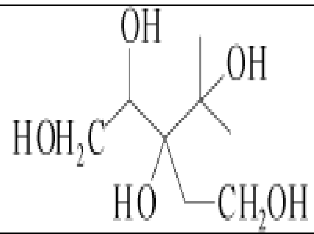
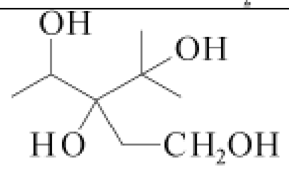
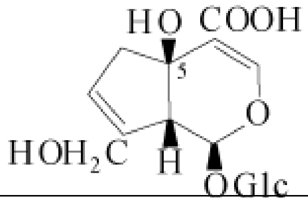
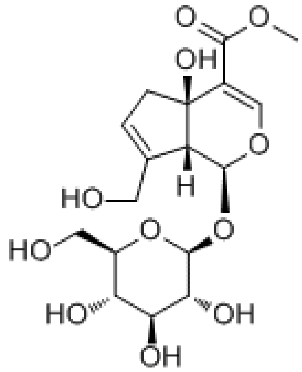
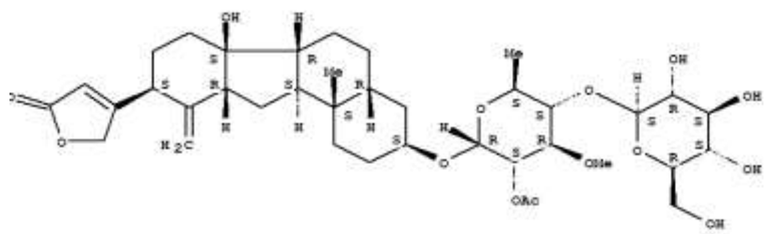
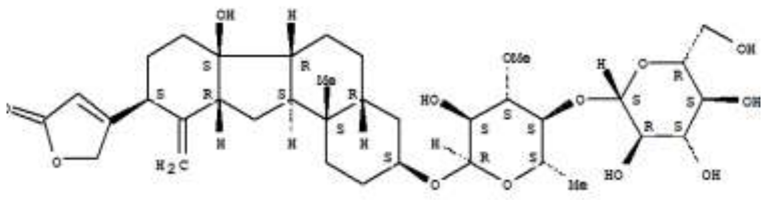
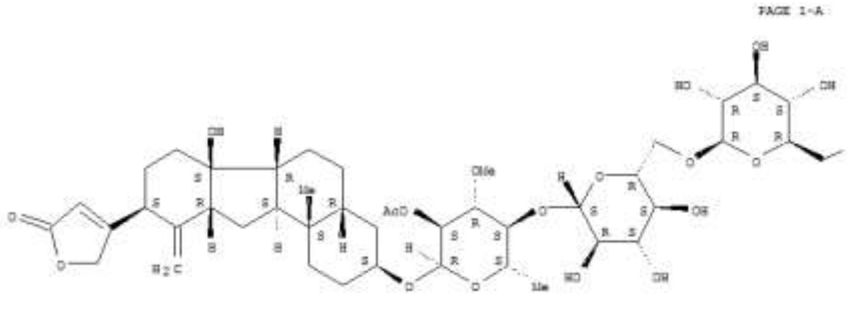
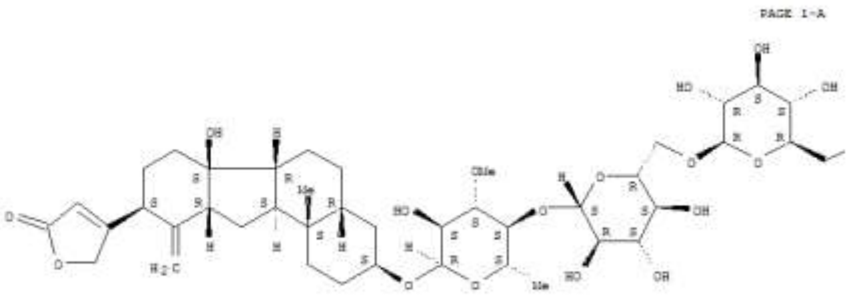
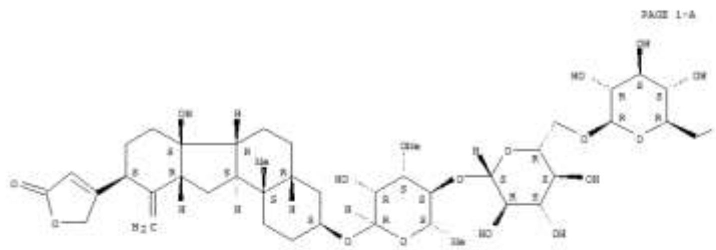
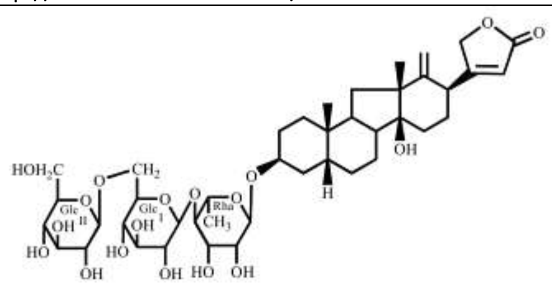
6859-20-7 : Ruvoside	
3371-93-5 : Nerifolin	
6859-20-7 : 3,14,19-Trihydroxycard-20(22)-enolide	
286951-03-9 : 5,12-Ursadien-3-ol; (3Î²,18Î±H)-form, Ac	
12-Ursen-3-ol; (3Î²,18Î±H)-form, Ac : 286951-04-0	

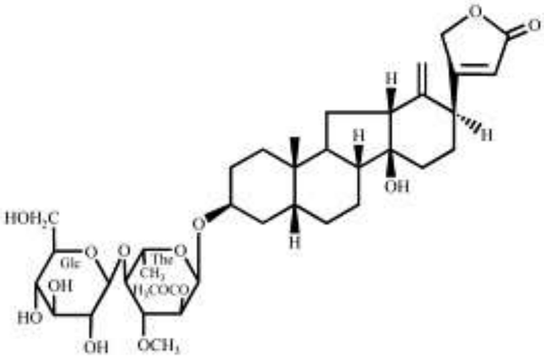
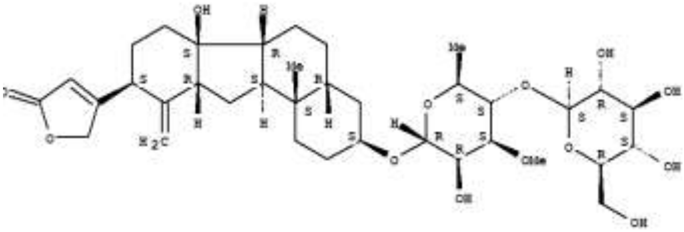
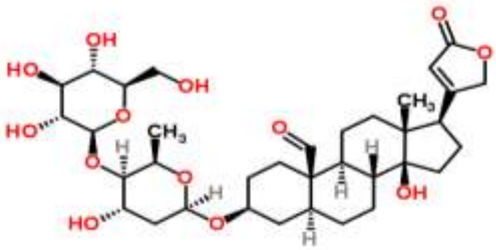
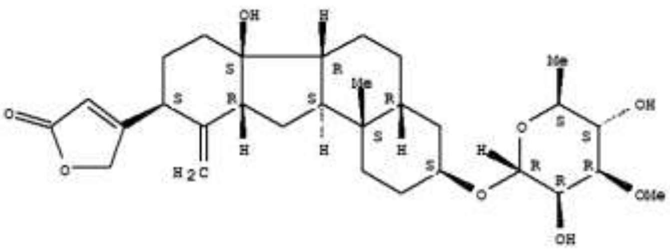
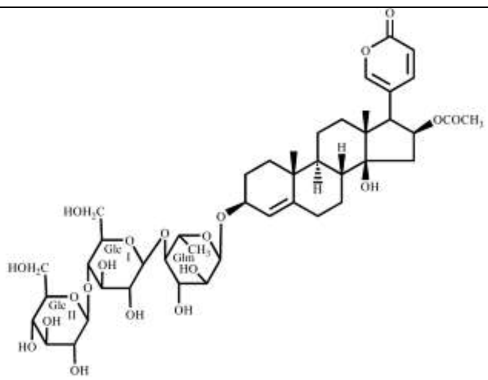
3,14,21-Trihydroxypregnan-20-one; (3,14,21-Trihydroxypregnan-20-one; (3Î²,5Î²,14Î²)-form, 3-O-[Î²-D-Glucopyranosyl-(1->6)-Î²-D-glucopyranosyl-(1->4)-6-deoxy-3-O-methyl-Î±-L-mannopyranoside], 21-O-Î²-D-glucopyranoside)	
74048-34-3 11,12-Epoxy-3-hydroxy-28,13-ursanolide	 (2α,3α)-*form*
3371-93-5	
6859-20-7 Thevereniin	
Quercetin 3-glycosides; Disaccharides, 3-O-[Î²-D-Glucopyranosyl-(1->2)-Î²-D-galactopyranoside]	 $C_{27}H_{30}O_{17}$

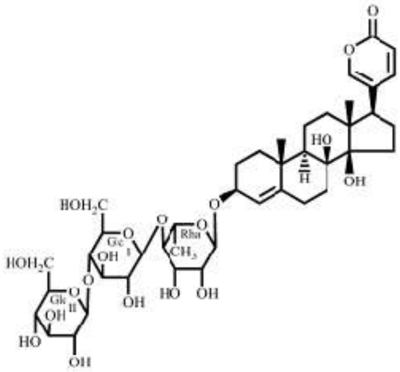
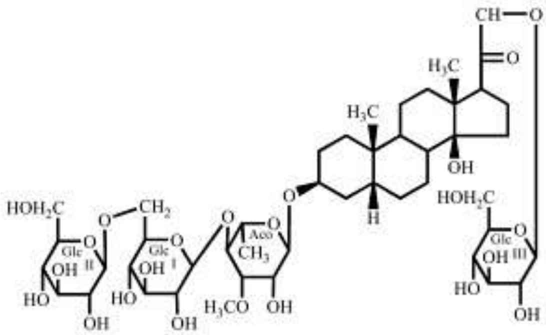
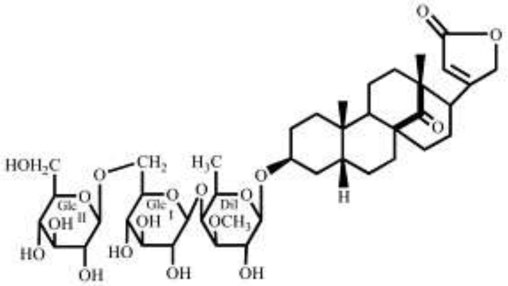
603-61-2: 3,3',5,7-Tetrahydroxy-4'-methoxyflavone	
366014-83-7 : Peruvianoside III	
168781-62-2 : Quercetin	
80164-75-6 : Thevefolin	
87315-09-1 : Thevefolic acid B	

Thevefolic acid A : 87315-08-0	
29781-29-1 : Theveside	
23407-76-3 : Theveside Me ester	
141365-10-8 - THEVETIOSIDE A	 http://www.guidechem.com/cas-141/141365-10-8.html
Ursan-28-oic acid: 74048-34-3	1-O-[Î²-D-Apiofuranosyl-(1->6)-Î²-D-glucopyranoside]  1 Quercetin 3-*O*-[*α*-d-apiofuranoyl(1–5)-*β*-d-apiofuranosyl(1–2)]-*α*-l-rhamnopyranosyl(1–6)-*β*-d-glucopyranoside

3-Ethyl-4-methyl-1,3,4-pentanetriol; 1-O-[Î²-D-Apiofuranosyl-(1->6)-Î²-D-glucopyranoside] : 182259-30-9	
182259-34-3	
188259-32-1	
29781-29-1: Theveside	
23407-76-3 : Theviridoside/ Theveside Me ester	 http://www.chemblink.com/products/23407-76-3.htm
141374-91-6 : Thevetioside E	 http://www.guidechem.com/dictionary/en/141374-91-6.html

141365-12-0 : Thevetioside C	 http://www.chemnet.com/cas/en/141365-12-0.html
141374-92-7 : Thevetioside G	 http://www.guidechem.com/cas-141/141374-92-7.html
141365-14-2 Thevetioside F	 http://www.guidechem.com/dictionary/en/141365-14-2.html
141365-15-3 Thevetioside H	 http://www.chemindex.com/141365-15-3-cas.html
$C_{41}H_{62}O_{18}$ / 197509-37-8 Thevetia Ahouia Saponin 2	

141374-91-6: Thevetioside E	 Spectroscopic data of Steriod Glycosides Volume 4
141365-13-1 : Thevetoside D	 http://www.guidechem.com/cas-141/141365-13-1.html
$C_{35}H_{52}O_{13}$ CHEIRANTHOSIDE III [172290-68-5]	 http://www.chemspider.com/Chemical-Structure.23311637.html
141365-11-9 Thevetioside B	 http://www.chemnet.com/cas/en/141365-11-9.html
$C_{44}H_{64}O_{20}$: Saponin 19	 Book: Spectroscopis Data on Steroids Glycocides

$C_{42}H_{62}O_{19}$ Saponin 9; 1178855-50-4	 Book: Spectroscopis Data on Steroids Glycocides
3371-93-5	 http://pubchem.ncbi.nlm.nih.gov/summary/summary.cgi?cid=11968835 http://www.chemspider.com/Chemical-Structure.4947016.html
C46H76O23: Thevetia Nerifolia Saponin 13	 Spectroscopic Data of Steroid Glycosides Vol. 5
C42H64O18:Oleaside F	 Spectroscopic Data of Steroid Glycosides Vol.6

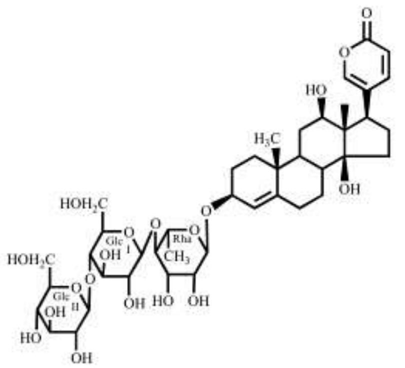
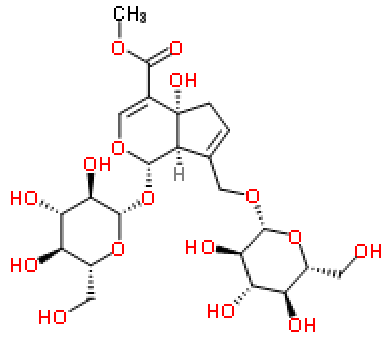
C42H62H19:	 Spectroscopic Data of Steroid Glycosides Vol.6
$C_{23}H_{34}O_{16}$	 http://www.chemspider.com/Chemical-Structure.8501078.html

Figure 1: Thevetia peruviana: अश्वाघना:the Goodluck Tree

Researchers, have characterized cardenolide triglycosides of neriifolin, acetylneriifolin and thevetin from its seeds. Its flowers have been investigated for the quercetin, kaempferol and quercetin-7-o-galactoside. Cardiac glycosides, sterols, iridoid glucosides, pentacyclic triterpenes and a cardenolide have been isolated from leaf extracts. Seven known compounds showed presence from fresh uncrushed leaves such as 1) neolupenyl acetate, 2) 11-oxo-urs-12-en-28-oic acid, 3) lupeol acetate, 4) oleanolic acid, 5) ursolic acid, 6) stigmast-5-en-7-one, and 7) β-sitosterol. Bark extract shows presence of four cardenolide glycosides; neriifolin, thevefolin, peruvoside, and (20S) – 18, 20-epoxydigitoxigenin α-L-thevetoside. Root extract shows presence of iridoids, theveside, theviridoside, and two new glucosides of theviridoside namely 10-O-β- D-Glucopyranosyl theviridoside and 3-O-β-D-Glucopyranosyl theviridoside [5].

Properties

Thevetia peruviana plant shows a diverse array of properties ranging from being a toxin to a *cardiotonic* [33]. Kernels of the plant exhibit toxicity primarily coming from cardiac glycosides present in the plant, which are primarily triosides or monosides of digitoxigenin. Thevetin found in seeds is a mixture of 2 triosides Thevetin A and Thevetin B in the 2:1 ratio. Monosides isolated from the seeds are neriifolin, cerberin, peruvoside, thevenerin, and perubosidic acid showed positive inotropic effect. Peruvoside has been a successful oral drug in the market for its digitalization activity. Thevetin mixture– A and B, cardiac glycosides, has been effective a decompensation cardiotonic [33].

Biological significance of the plant

Flavonoids, steroids and terpenoids, found in thevetia peruviana are the prominent secondary metabolites that have resulted into anti-inflammatory, anti-bacterial and anti-fungal activity. Secondary metabolites like Quercetin, Kaempferol found in the flowers; Oleanic acid, Ursolic acid, and β-sitosterol isolated from fresh crushed leaves have shown the presence for these activities.

Flavonoids and tannins in *Thevetia peruviana* are possessing antimicrobial activity. The antimicrobial activity in a flavonoid is primarily due to its ability to complex with extracellular and soluble proteins that leads to binding with a bacteria cell wall, while that of tannins is related to their ability to inactivate microbial adhesion enzymes and cell envelop proteins.

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