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CLASSICAL REVIEW OF *PITA KARAVIR*(*THEVETIA NERIIFOLIA JUSS. EX STEUD*)

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ABSTRACT

The yellow oleander *Thevetia neriifolia* Juss. or *Thevetia peruviana* Merr. or *Thevetia peruviana* Schum., is commonly a garden plant in India and many other parts of the world. It grows in and around houses, hutments and on the roadside and is often seen forming protective hedging material around gardens. *Pita Karavir* (*Thevetia neriifolia*) plant is having more importance in *Agadtantra*. Poisoning incidences are more common in southern parts of India and Sri Lanka. As commonly available, chances of accidental poisoning are more. Its uses in cosmetics, as like against stretch marks could open new doors in field. So new insights towards this plant should be developed. So in this article efforts have done to compile data available about *Thevetia neriifolia* through available texts of *Ayurved*, and all other available modern literature.

Keywords : *Thevetia, Karavir*, Cardiac poison, *Hrudya*, *Kharajahar*, Hayamar

INTRODUCTION: The yellow oleander *Thevetia neriifolia Juss. ex Steud.* or *Thevetia peruviana* Merr. or *Thevetia peruviana* Schum., is commonly a garden plant in India and many other parts of the world. it grows in and around houses, hutments and on the roadside and is often seen forming protective hedging material around gardens. (Kumar, C. et al. (2017).. *Research Journal of Pharmacology and Pharmacodynamics*, *9*(2), 93–96.)

The main toxic effects of glycosides found in *Thevetia neriifolia* are related to its digitalis-like action on the heart and severe gastrointestinal irritation.

Poisoning is presented by numbness, burning sensation of the mouth, nausea, vomiting, abdominal pain and diarrhea. Also other symptoms can be found are drowsiness, coma, occasional convulsions, and cardiac arrhythmias. Ventricular fibrillation is the ultimate cause of Death.

Diagnosis is done by assessing history of consumption and the presenting symptoms. Investigations include estimation of Cardiac glycosides in the blood by competitive immunoassay, monitoring serum potassium concentration, Monitoring of ECG and renal function is important. Remnants of seeds can be identified in vomitus or gastric aspirate.

Being commonly available, chances of poisoning by *thevetia neriifolia* become more also it has got significance in treatment of many diseases, which cannot be cured by routine medicines.

Hence attempt is made here to present available literature about *Pita Karavir* Plant to enlighten ignored areas of it.

AIMS & OBJECTIVES

1. To Collect and Present all available literature about plant *Thevetia neriifolia*.
2. Presentations of available Data

MATERIALS & METHODS

Classical *Ayurvedic* literature was Studied through available *Samhitas*, commentaries and *Nighantus*. Modern literature was collected from Modern books, journals and internet. All information collected was subjected to analysis and further interpretation drawn from it.

OBSERVATIONS & RESULTS

Historical Review

Various ancient texts described *Karavir* as follows

Table No. 1 - Historical review

Rugveda	*Hrudya vanaspati*	
Maitrayani	*Srekaparna*	
Kathakasamhita	*Srekaparna*	
Samavidhana Bramhana	used for brushing the teeth (sa. 2/4/1)	
Mahabhasya	*Karavira* flowers are described	
Kautilya Arthashastra	described along with other ingredients , it was used for making "*Madanayoga*".	
(Mruchhakatik102)	necklace of flowers of *Karavir* was given to person who get punished as death sentence	
Mahabharat Aaranyak-parva adhyay115	*Kanchan Shaila* is called as *Karaviraban*	
Charak Samhita	*Cha.Chi. 7/104,105*	reference about *Shveta Karavira*
Ashtang Hriday	*A.H.Chi.19/61*	
Charak Samhita	*Cha.Chi. 23/11*	The roots of a plant *karavira* are mentioned as poisonous
		Advices Karavira for bathing and internal administration also.
Sushruta Samhita	*Su.Chi.29/5, 13, 20, 26*	quoted *''KARAVIRA SOMA''*,] as one of the varieties of soma
		Indicated *Karavirakshara* in *Ashmari* treatment.
Vagbhata	*A.H.Sha.1/61*	Treatment of Itching and Stretch Marks of Pregnant Women.
	A.H.U.36/70	*Karaviraadi Agada*- For Treatment of Snake Bite
		Quoted it under *Upavisha* group.
Sharangadhara	various therapeutic application of *Karavira*. *Karavirmula Lepa*(U.11/105*); Karaviraadi Tailam for Kesha Shatana*	
Chakradatta	*Kushtha Chikitsa (Visha Tailam; Vajraka tailam; Mahatrunaka tailam; karaviradya and Shvetakaraviradya Tailam) and Vranashotha Chikitsa (Chirbilvaadi Lepa)*	
Dhanvantari Nighantu Bhavaprakasha Nighantu.	advised external application	
Modern Period	research has been conducted on Seed & root of *Karavira* related to its Toxicological action, Physical and chemical properties and other standardization criteria	

Names in Different Languages

TABLE NO. 2 - Names in different languages[i]	
Sanskrit	*Karavira*
Hindi	*safed kaner, lal kaner.*
Bengali	*Shveta karavira, lal karavira.*
Marathi	*Karavir, Kalhher, Patari, Kanar- tamvadi.*
Kannada	*Vakana linge, Kangana linge.*
Tamil	*Kanel chettu.*
Arabic	*Sumula, Himara dakhali.*
English	*Oleander.*
Latin	*Nerium oleander.*
Pharasi	*Kharajahar*

Names in Different Regions

TABLE NO. 3 - Names in different Regions[ii]	
Bombay	*Chinakarab, Kokilphul, Kolkaphul.*
Deccan	*Pila kaner, Pilephul ka kaner.*
Burma	*Hpayoungban, Molamiyaipan.*
Gold coast	*Exile oil plant, Milk Bush.*
Gujarati	*Pila kanir, Pilokanera.*
Madras	*Manjalalari.*
Malay	*Guinnyeh, Maloaie, Mallaye.*
Malayalam	*Panchaarali, Arali.*
Mundari	*Marangakanaili, Kaili.*
Telugu	*Ganneru (Pachchaganneru).*
West indies	*Jaca, Ahouai, Abia de matto.*
Arab	*Sumul-himar.*
Bengal	*Karabi.*
Kannda	*Kanagila.*
China	*Kiah chuh-au.*
Telugu	*Kasturi patte.*
Latin	*Nerium odorum, Nerium oleander.*

*The meaning of Arabi Sammul-himar and Pharasi Kharajahar is *Gardhabha*(Donkey) *visha*. The meaning of word *Arabi Sammulmar* is Snake Venom[iii].

Synonyms of *Karavir*[iv, v, vi, vii, viii, ix, x, xi]

TABLE NO. 4–SYNONYMS OF *KARAVIR*				
	Synonyms **of *Shveta Karavir:***		**Synonyms of *Rakta Karavir***	**Synonyms of *Pita Karavir***
1)	*Prathihasa*	*Tungari*	*Raktapushpa*	*Peeta Karavira*
2)	*Meenakakhya*	*Nakharavha*	*Rakta Karavir*	*Peeta Prasav*
3)	*Abjabeejabrith*	*Sthaladikumbuda*	*Rakta prasav*	*Sugandhikusuma*
4)	*Karavir*	*Sthalakumuda*	*Chanda*	*Padya*
5)	*Kanavira*	*Divyapushpa*	*Chandanta*	*Patalika*
6)	*Svetapushpa*	*Harapriya*	*Chandaka*	*Peetapushpa*
7)	*Shvetakunda*	*Haripriya*	*Chandataka*	*Alpapushpika*
8)	*Shatapushpa*	*Gouripushpa*	*Chandal*	
9)	*Shatakumbha*	*Siddhipushpa*	*Vichandika*	

10)	*Shatakunda*	*Gandharva*	*Prachanda*	
11)	*Shataprasa*	*Suraksheta*	*Krura*	
12)	*Ashvamaraka*	*Chandata*	*Bhutadravi*	
13)	*Asvarohaka*	*Prachanda*	*Laguda*	
14)	*Ashvarodhaka*	*Mahavira*	*Ganeshkusum*	
15)	*Asvantaka*	*Veera*	*Chandikusum*	
16)	*Ashvaghna*	*Veeraka*	*Ravipriya*	
17)	*Ashvanashaka*	*Kurida*	*Gulmakasva*	
18)	*Ashvaha*	*Kunda*	*Karavirak*	
19)	*Ashvamohaka*	*Sankundra*	*Gulmaka*	
20)	*Hayamaraka*	*Sakunda*		
21)	*Hayaghna*			
22)	*Hayari*			
23)	*Hayamara*			

Classical Categorisation

TABLE NO. 5 – CLASSICAL CATEGORISATION

Text	Gana
CharakaSamhita[xii]	*Kusthaghna; Tikta skandha; Moola visha varga; Tikta varga.*
SushrutaSamhita[xiii]	*Laksadi gana; Shiro virechana varga; Moola visha varga; Tikta varga*
Vagbhata[xiv]	*Laksadi gana.*
B.N	*Guduchyadi varga; Vishopavisha varga.*
D.N.	*Karaviradi chaturda varga; Upavishagana of Misrakadi sapthamovarga.*
R.N.	*Karaviradi varga.*
K.N.	*Avasishta amsha of Aoushadi varga.*
Sha.N.	*Guduchyadi varga.*
Sho. N.	*Karaviradi varga* *Paniya varga.*
M.N.	*Haritakyadi varga.*
N.A.	*Kutajadi varga.*

Types of *Karavir*

TABLE NO. 6 – TYPES OF *KARAVIR*

Reference	Types	Names
Sho. N./ M.N./ D.N.	2	White; Red
K.N./ Bh.N./ modern	3	White; Red; Yellow
N.A./ R.N.	4	White; Red; Yellow; Black
Sha. N.	5	White; Red; Yellow; Black; Pink
G.A.	6	Alba; Rubra; cornea; Florepleno alba; Florepleno corneo; Florepleno rubra

**Samhitas* and *Nighantus* mainly described 2 varieties, visually., white and red varieties which are identified as *Nerium indicum* botanically, this possess 2 colours of flowers. The yellow variety is *Thevetia peruviana* (or) *Thevetia neriifolia* botanically; while the black (*Krushna*) variety is not known. It may be the purplish tinged flowers of *Thevetia peruviana* which occur in some places.[xv]

Macroscopical Factors[xvi]

ROOT:- highly branched; greyish in colour with long irregular streaks.

STEM:- branched, greyish or greyish green in colour with similar types of streaks on the bark surface.

BARK- appears soft,Silvery grey white.

LEAVES:- are dark green in red flowered variety and light green in white variety with size approx. 17cm long and 1-3cm wide, exstipulate, petiolate(short petiole), whorled and each whorl having 3 layers, linear, lanceolate, entire, acuminate, thick and coriaceous, unicostate venation, reticulate is stout and run parallel to each other,

BOTANICAL DESCRIPTION[xvi]

Karavira has varieties depending to the colour of flowers as Red, Yellow, White, etc. Its Leaves are long and comparatively thick. Fruits of Red and White variety are long, 4 to 6 inch in length and seeds are many. The fruit of Yellow variety is round and light green colored (unripe) or grey (ripened fruit) and has 2 seeds of light yellow colour. It is poisonous. *Bhavaprakasha*. It is a large evergreen, shrub with milky juice.

LEAVES:- They occur in 3 whorls, shortly stalked, coriaceous, 6-20*1-3 cm, linear, lanceolate, acuminate, taper to short petiole, dark green and lustorous above, stout midrib with numerous nerves which spread horizontally.

FLOWERS:- are Red (rose colored) or White in color, fragrant. They appear in April to June, inspite are present throughout the year while fruits appear in the cold season.

CALYX:- Lobes are lanceolate.

COROLLA:- with rounded lobes, 2.3 to 3cm in diameter, fragrant,.

FILAMENTS:- Hairy, anthers appendages are double as length of the cells, they join together adnate to stigma. Cells are long and spurred at base.

FRUIT:- somewhat cylindrical 15-17.8 cm in length, rigid to touch, appressed longitudinally. (Color: yellowish green to light brown in Nerium oleander).

SEEDS: - numerous, small, tipped with coma of light brown hairs, with flat Cotyledons.

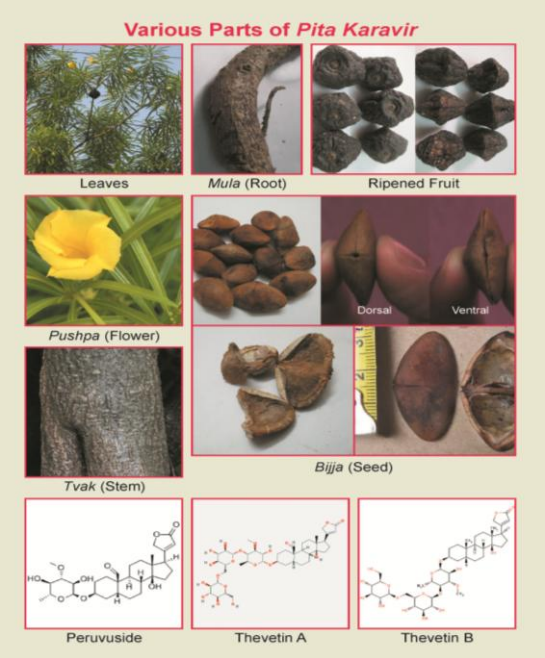
Habitat [xvi]

Grown as an ornamental tree in gardens. This plant belongs to Central & South America, but nowadays frequently grown throughout the tropical and subtropical regions.

Cultivation[xvi]

It is widely cultivated in gardens for its elegance and shady foliage and flowers.

It requires little attention. It is grown from seeds and cuttings, transplants well, and can endure drought and frost to some extent. Since it is not browsed by cattle or goats, yellow oleander may be used for afforestation in the moister tracts. Sometimes these plants are grown along canal-bunds to provide leaves for the development of compost.



Distribution[xvi]

Nerium indicum Linn. –found in the Himalayas from Nepal to Kashmir at up to 1,950m and in northern gangetic plain and parts of Madhya Pradesh. It is grown in gardens all over India. Nerium is native of Mediterranean region extending upto Iran. It is often grown in Indian gardens for ornamental purpose and at fence.

Thevetia neriifolia is native of South America and West Indies, often planted in India.

Karavira is found in Himalaya, Nepal to Kashmir, Uttar Pradesh, Punjab, Baluchistan, Dakshina Bharat, china and Japan. *Karavira* (*Shveta and Rakta*) found in almost in all places of South India and Uttar Pradesh. Yellow variety is grown in almost all places, more in hot climate regions.(*B.N.*).

Rasa Panchaki,iv,v,vi,vii,viii,ix,x,xi

TABLE NO. 7 –Rasa Panchak of Karavir

RASA	***GUNA***	***VIRYA***	***VIPAKA***	***PRABHAVA***
Katu, Tikta, Kashaya.	*Teekshna, Laghu.*	*Ushna*	*Katu*	

Actionii

TABLE NO. 8 – Action of Karavir

Externally	**Internally**
Useful to Eyes	Poisonous
Useful against Itching	
Useful against Skin Disorders	
Wound Manangement	
Curates Infections in wounds	
Beneficial for Heart	
Increases Urine Volume	
Used against Fever	
Aphrodisiac	

TABLE NO. 9 – Action of *Karavir* Part Wise	
Part	**Action**
fixed oil	pure is quite inert
Bark	bitter and powerfully cathartic, antipyretic in small doses, 2gm of powdered bark - equal to an ordinary dose of Cinchona, but it's use is attended with considerable danger. 30-60 ml of tincture – emetic
Root and the root bark	powerful diuretic and cardiotonic like Strophanthus and Digitalin its infusion is used in cardiac systole and in dropsy
Oleandrin	if injected hypodermically, it reduces heart rate from 75 or 80 to 10 or 12, if continued for sometime the heart ceases to beat and with it the respiration
Milky juice of *Thevetia neriifolia*	highly poisonous
kernel	powerful acro-narcotic poison
Antihelminthic, Antipyretic and at Antiseptic. Pharmacological study has proved it as cardiotonic.	

Indications

TABLE NO. 10 – Indications of *Karavir*	
REF.	**INDICATION**
Charaka	*Kusthaghna dashaimani*
D.N.	*Kandu, Kushtha, Charmaroga and netraroga.*
B.N.	*Karavira* is useful in *Kushtha, Vrana, Netra kopam*
S.N.	*Shveta karavira* is useful in *Prameha, Kandu, Kotha, Krumi, Visphota, Jvara and Netraroga*
N.A.	*Karavira* is used in treating *Kushtha, Jvara* and is poisonous
M.N.	Both the white and red varieties are said to be of use as on external application to swellings, *Kushtha* and various skin diseases. also beneficial in *Jvara*, *Netra roga, Vrana*. The pink variety as regarded in "Nighantu Ratnakara", removes *Shirashula* and overcomes ill effects of *Vata* and *Kapha*. Yellow and black varieties are having similar medicinal values as of white variety.
Sha. S.	*Upadamsha*

Therapeutic Uses

TABLE NO. 11 – Therapeutic Uses of *Karavir*			
Ref.	***Adhikar***	**Yoga name**	***Rogaghnata***
CHARAK SAMHITA			
Cha. Su.3/3-7	*Bahiparimarjan Chikitsa*	*Aaragvadhaadi Lepa*	*Kushtha, Kilas, Indralupta, Various skin diseases.*
Cha. Su.3/10-11	*Bahiparimarjan Chikitsa*	*Kushthaadi Churna*	*Dadru, Kandu, Kitibha, Pama, Vicharchika.*
Cha. Su.3/14-16	*Bahiparimarjan Chikitsa*	*Haridraadi Lepa*	*Various skin diseases.*
Cha. Su.3/17	*Bahiparimarjan*	*Aaragvadhaadi Lepa*	*Kushtha.*

	Chikitsa		
Cha. Su.4/13	*Kushtha*	*Kushthaghna Mahakashaya*	*Kushtha*
Cha. Chi.7/56-57	*Kushtha*	*Kushthaghna Pradeha*	*Stabdha, Supta, Asvedana, Kandu in Kushtha.*
Cha. Chi.7/93-94	*Kushtha*	*Karaviraadi Lepa(root of Shveta Karavir)*	*Kushtha*
Cha. Chi.7/104	*Kushtha*	*Svetakaraviradya Taila*	*Kushtha*
Cha. Chi.7/105	*Kushtha*	*Svetakaravirapallavadya Taila*	*Kushtha, Kandu.*
Cha. Chi.7/111-114	*Kushtha*	*Kanakakshiri tailam*	*Mandala Kushtha,(Bahya)krumi, Kandu.*
Cha. Chi.7/129	*Kushtha*	*Karavir Kwath*	*Bath & internal administration in Kushtha.*
Cha. Chi.21/87	*Visarpa*	*Triphalaadi Pradeha*	*Kaphaja Visarpa*
Cha. Chi. 23/29	*Visha Chikitsa*	*Karavir kalka(leaf)*	*Anjana in Akshi Uparodha.*
Cha. Chi. 25/87	*Vrana*	*Vranaropana Kashaya*	*Vranaropana*
Cha. Chi. 26/266	*Paalitya*	*Dugdhika Yoga*	*Palityahara*
SUSHRUTA SAMHITA			
Su.Su.37/12	*Mishraka Adhyaya*	*Karavir Kwath*	*Vrana Shodhana*
Su.Su.38/64-65	*Dravya Sangrahaniya*	*Laakshaadi gana*	*Krumi, Kushtha, Dushtavrana.*
Su.Su.39/6	*Sanshodhana shamaniya*	*Karavir root*	*Shirovirechana Dravya*
Su.Chi. 7/23	*Ashmari*	*Karavir Kshar*	*Sharkara*
Su. Chi.8/50-57	*Bhagandara Chikitsa*	*Syandana (Doshaharaka) Taila*	*Bhagandara, Vrana-Shodhana & Ropana, Savarnikarana.*
Su. Chi.9/10	*Kushtha*	*Karavir Lepa*	*Kushtha*
Su. Chi.9/27	*Kushtha*	*Shvitrahar Lepa(1&2)*	*Shvitra*
Su. Chi.9/52	*Kushtha*	*Karavir-Vidanga Lepa*	*Krumi eaten part in Kushtha*
Su. Chi.15/39	*Upadamsha*	*Karavir Patra*	*Upadamsha*
Su.U.47/31	*Panatyaya Chikitsa*	*Hriberaadi Lepa*	*Ekanga Shopha*
ASHTANGA HRUDAYA			
A. H. Sha. 1/61	*Garbhini*	*Karavir Patra Siddha Taila*	*Garbhini Kandu & Kikwis*
A.H.Chi.17/25	*Shvayathu*	*Karavira Lepa*	*Ekanga Shopha*
A.H.Chi.18/14	*Visarpa*	*Triphalaadi Lepa*	*Kaphaja visarpa*
A.H.Chi.19/61	*Kushtha*	*Karaviraadi Kwatha (applied as Lepa)*	*Kushthaghna*
A.H.Chi.19/62	*Kushtha*	*ShvetakaravirMoolaadi Lepa*	*Kushtha*

A.H.U.24/29	*Shiroroga*	*Karavir Swarasa (applied after Siravyadha)*	*Indralupta*
A.H.U.24/38	*Shiroroga*	*Karavir & Dugdhika processed in milk*	*Paalitya*
A.H.U.36/70	*Sarpavisha Pratishedha*	*Karaviraadi Agada (Karavir flower & root as ingredient)*	*Agada*
OTHERS			
B.P.Chi. 51/35	*Upadamsha*	*Karavir Moola Kalka (applied as Lepa)*	*Upadamsha*
Cd. Vranashotha Chi/22-23		*Chirbilvaadi Lepa (Karavir as ingredient)*	*Vrana Daarana*
Cd Kushtha Chi/124-131		*Mahatrunaka Taila (Karavir as ingredient)*	*Various Skin disorders*
Cd Kushtha Chi/132-134		*Vajraka Taila (Karavir as ingredient)*	*Kushtha, Naadi Vrana*
Cd Kushtha Chi/146-149		*Visha Tailam (Karavir as ingredient)*	*Vrana vishodhana, Kandu, Kacchu.*
Cd Kushtha Chi/150		*Karaviraadya Tailam*	*Kushtha*
Cd Kushtha Chi/		*Shvetakaraviraadya Tailam*	*Kushtha*
Cd.	*Pama*	*Karavir Swarasa Siddha Taila*	*Pama*
Cd.	*Netrakopa*	*Karavir salila*	*Netrakopa*
R.T.494/495		*Karavir*	*Upadamsha, vrana, Netrabhishyanda.*

Special Formulations

TABLE NO. 12 – Special Formulations of *Karavir*
1. Karaviradya taila : Bhaishajya Ratnavali
2. Karaveeradi tailam : Vaidya chintamani
3. Karaveeradya tailam : Vaidya chintamani
4. Vajratailam : Vaidya chintamani
5. Karaveeradilepam : Astanga hrdayam
6. Shveta Karaveeradi lepam : Astanga hrdayam
7. Yekanga sophahara lepam : Astanga hrdayam(ci.17/25)
8. Palita rogahara lepam : Astanga hrdayam(U.24/35)
9. Garidamalaku chendanadi tailam : Astanga hrdayam
10. Jyotishmatyadi tailam : Astanga hrdayam(U.28/34)
11. Mustadi churnam : Astanga hrdayam (Ci.19/67)
12. Sleshmavisarpahara lepam : Charaka samhita (Ci.21/87)
13. Vishaharnjana : Charaka samhita)Ci.23/69)
14. Vishatailam : Vydya chintamani
15. Pallavadya tailam : Materia Medica by Nadkarni
16. Shveta karaveeradya tailam : By Charaka as quoted in *chakra data*
17. Karaveeramula lepa : Saramgadhara samhita (U.11/.105)
18. Chermaroganasaka tailam : Vanoushadi chandrodaya
19. Vaatanasaka tailam : Vanoushadi chandrodaya
20. Kasisadi tailam : API

Parts Used (*Prayojya Anga*)

TABLE NO. 13 – Parts Used of *Karavir*	
1. Charaka samhita	*Moolam, Moolatvak.*
2. Susruta samhita	
3. Nighantu Aadarsha	*Moolatvak, Patram, Pushpam.*
4. Raja Nighantu	*Moolatvak, Patram.*

*Though *Charaka* and *Sushruta* have mentioned *Moola* and *Moolatvak* as useful parts of *Karavira*, in treatment of *Kushtha* "*Karavira panchanga Kwatha*", is beneficial.
**Sushruta* has mentioned *Karavira* leaves in *Ashmari* and *Upadamsha*

Dosage

Rakta Karavir mula Churna - 30-150mg
Tincture - 10-14drops

Chemical Composition[xvixvii]

TABLE NO. 14 – Chemical Compositionof Karavir	
Nerium indicum	***Thevetia neriifolia***
Oleandrin ($C_{32}H_{48}O_9$)	Cerberoside (Thevetin-B)
Karabin ($C_{21}H_{19}O_6$)	Thevetin A
Neriodorin($C_{22}H_{32}O_7$)	Thevetin
Neriodorein($C_{23}H_{34}O_{11}$)	Thevotoxin
Neriodin	Peruvoside
Nerium-D	Ruvoside
Scopolin	Thevefolin

Scopoletin	Nerifolin
Rosagenin	Cerberin
Tannin	Peruposide
Fenolinic acid	Peruvosidic acid
Aromatic oil	Theveneriin
Rutin	Theveside
Glycosides	Theviridoside
Potassium salts	Uridoside
Yellow colored stable oil	
Crystal wax	
Flobefin	
Red colouring agent	

The toxin(s) of *Thevetia neriifolia:*

TABLE NO. 15 –Toxins of *Karavir*

Description	chemical structure	Mol. Wt.	
Thevetin A	$C_{42}H_{64}O_{19}$	872.93	CAS number: 37933-66-7
Thevetin B	$C_{42}H_{66}O_{18}$	858.95	CAS number: 11005-70-2
Peruvoside	$C_{42}H_{44}O_9$	548.65	CAS number: 1182-87-8

Glycosides Of *THEVETIA NERIIFOLIA*[xvi,xviii]

Thevetin, the first trioside to be isolated, is the major component of the seeds. It was subsequently found to be a mixture of two triosides, viz. thevetin A and thevetin B (cerberoside). A small proportion of another trioside, 2'-O-acety cerberoside is also associated with thevetin. The separation of thevetin into pure components, thevetin A and cerberoside has been achieved by partial chromatographic and countercurrent techniques by several workers ; by the countercurrent technique, thevetin A and cerberoside were obtained in a ratio of 1 : 2. The monosides separated from the seeds include neriifolin, cerberin (2'-O-acetylneriifolin), peruvoside, theveneriin (ruvoside), and peruvosidic acid (perusitin). These glycosides do not appear to occur as such in the seeds and are presumably formed as a result of enzymic hydrolysis of the triosides.

On partial hydrolysis, thevetin A yields the monoside peruvoside from which theveneriin (ruvoside) can be prepared by reduction; peruvoside and theveneriin are aldehyde and alcohol products. a mixture of cerberin and 4'-O-acetylneriifolin is obtained by careful acetylation of *neriifolin*. Oxidation of peruvoside with CrO_3 give peruvosidic acid.

Peruvoside

Of all the *Thevetia* glycosides, Peruvoside is the most important, and a large amount of work has been done on its pharmacology, toxicology and clinical aspects and there are definite indications that it is among the most useful of cardiac glycosides.

Preliminary work on the cardiotonic effect of peruvoside showed that it exerts quick and powerful positive inotropic effect in experimental animals.

Using the heart-lung preparation of dog, it was later found out that in the failing heart, peruvoside is almost as quick-acting and as potent as the standard drug ouabain.

In therapeutic doses, it produces a fall in right atrial pressure and a rise in the

cardiac output. Similar results were obtained on pig's heart-lung preparation.

In experimental heart-failure in anaesthetized cats and dogs, a strong positive inotropic action was observed with peruvoside when administered intravenously; the pulse rate was restored to the normal, the ventricular function improved and there were no pathological ECG changes.

Comparison with ouabain and proscillaridin showed that peruvoside was much more potent than proscillaridin in its inotropic effect. Whereas the inotropic effect and therapeutic dosage-range of peruvoside were similar to ouabain, peruvoside differed from the latter in its lower toxicity and normalizing effect on the Heart rate.

The acute and subacute-toxicity studies indicate that peruvoside has a high therapeutic index and the electrocardiographic changes produced by it closely resemble those seen with other cardiac glycosides. Acute toxicity studies showed that the order of sensitivity to peruvoside in different animals was in the following descending order : dogs, cats, pigeons and guineapigs. The usual mode of death with a toxic dose was ventricular fibrillation resulting in cardiac arrest.

All the reports of clinical trials with peruvoside from different centres indicate that the drug has a quick action when administered intravenously, dependable absorption and action when administered orally, and low, acute and cumulative toxicity. The drug can be used in patients with liver and kidney diseases. Among the cardiac glycosides currently being used most commonly are digoxin for oral administration and ouabain (G-strophanthin) by intravenous route. Peruvoside has been reported to be more advantageous than both these drugs. The advantage over ouabain was its suitability for intravenous as well as oral administration and hence its usefulness in treating acute and chronic cardiac insufficiency; and the advantage over the digitalis glycoside was the comparatively small alterations of the ECG produced by it in therapeutic dose. Another advantage of peruvoside on these drugs is low toxicity.

Thevetin & Other Glycoside

Thevetin has been the subject of intensive study because it was the first glycoside of *Thevetia* to be isolated and for long thought to be a pure compound. The glycoside was reported to have a digitalis-like effect. It has been observed that thevetin is practically identical in effect with ouabain and about one-eighth as potent, the lethal dose for cat being 0.85 mg. per kilogram. It has effectively been used clinically in cases of cardiac decompensation and in the tachycardia of thyroidism. However, the effective dose is rather close to the toxic dose.

Thevetin is present in kernels of seeds in 3.6 to 4 percent as shown by physiological assaying[xix]..

Thevetin A is reported to be less potent than thevetin. As a cardiac glycoside, the potency of neriifolin is only moderate. Cerberin is even weaker than that of neriifolin. Cerberoside is one of the weakest of the Thevetia glycosides in its cardio tonic effect. Theveneriin, a minor component of the seeds, is a quick-acting glycoside with low toxicity by the parenteral route, but its absorption from the gastro-intestinal tract is poor and erratic, and it does not offer any significant advantage over the currently available range of cardiac glycosides.

Shodhana of Karavir[xx,xxi,xxii,xxiiixxiv]

TABLE NO. 15 –Shodhana OF Karavir	
Samanya Shodhana	**Vishesh Shodhan**
Godugdha	Godugdha
	Gomutra

Karavira is purified, if it is steamed in cow's milk for upto 3 hours by using *Dolayantra*.

Toxicity of Thevetia neriifolia(Kumar et al., 2017)

Active principles: Thevetin, Thevitoxin, Cerberin, Thevetin A, Thevetin B and Peruvoside.

Fatal dose: consumption of 8-10 whole seeds.

Fatal period: Upto 24 hours.

Toxicity

Adults: The kernels of about 10 fruits may be fatal

Children: The kernel of one fruit may be fatal.

Signs and Symptoms:-(Bisht 1965)

MANIFESTATIONS		PERCENTAGE OCCURENCE		
		Mild Toxicity	Moderate Toxicity	Severe Toxicity
SYMPTOMS other than cardiovascular manifestations	Vomiting	90	50	77
	Restlessness	40	65	75
	Abdominal Cramps	10	20	6
	Diarrhoea	8	-	-
	Salivation	3	4	-
	Tingling in mouth	3	-	-
	Nausea only	2	-	-
	Miscellaneous			
	Sore Throat	2	-	-
	Giddiness	2	-	-
SIGNS	Bradycardia	56	60	63
	Arrhythmia	35	50	55
	Hypotension	23	54	77
	Delayed Reaction	-	25	36
	Tachycardia	-	8	18
	Shock and collapse	-	5	63
	Semi consciousness	-	5	9
	CNS Affection	-	5	9

ECG Changes(Kumar et al., 2017)

'P' wave changes which may be in form of absent 'P' waves, or grossly distorted 'P' waves.

P-R interval prolongation.

ST segment changes in the form of St depression.

Irregularity in rhythm, the most common of which is non respiratory sinus arrhythmia.

Different types of heart block including I degree heart block(which is commonest), sinus arrest with nodal escapes, Wenchebach's phenomenon, bi-directional S.A.-A.V. heart block, bundle branch block and complete heart block with Strokes-Adams syndrome.

Tachycardia which may be supraventricular tachycardia, ventricular tachycardia or atrial flutter.

Fibrillation which may be atrial fibrillation or ventricular tachycardia (seen in the terminal stages).

The biochemical changes most frequently seen are hyponatremia, dominant hyperpotassemia, huperchloraemia, normal serum calcium and a dominant acidosis**.**

Death due to poisoning may result because of peripheral vascular failure (which is most common cause), arrhythmias and sometimes severe gastro-intestinal disturbances leading to fatal acidosis.

Significant changes are seen in almost all the organs of the body during post-mortem examination of the cases dying of yellow oleander poisoning. The most constant feature is the presence of gross congestion in the organs. The heart is often seen to be dilated and the inflammation of the splanchnic vessels is often a significant feature.

Thus the features of yellow oleander poisoning vary with the degree of toxicity, whether mild, moderate or severe. Most commonly the features involve the cardiovascular system and the gastrointestinal tract.

Diagnosis

Diagnosis can be made by history of consumption, circumstantial evidence and the clinical presentation. Glycosides can be found in the blood by competitive immunoassay. The serum potassium concentration needs to be be monitored along with ECG, and renal function test. Remnants of seeds, vomitus or gastric aspirate should be collected for identification purposes

Medicolegal Aspect

Suicide is the common feature among villagers. Girls in certain parts of India use the root as a decoction for this purpose.

Also the root is commonly used locally and internally for procuring abortion.

Accidental poisoning can happen sometimes, when use of any part of the plant is done for other purpose like to reduce swellings or the decoction of leaves is used internally as a remedy for veneral diseases or when paste of the root is used in treatment of cancerous condition and other growth.

Homicide with *Thevetia neriifolia* is rare. The use of *Thevetia neriifolia* as a cattle poison has been recorded.

Research

- The oil from seeds of *Thevetia neriifolia* has been chemically examined by Bhattacharya and Ramaswami Iayar [xxv].
- Glucoside has no action on digestive enzymes. It has little or no direct effect on respiration. Glycoside, on account of its cardiotonic properties, should be a potent therapeutic and toxic limit seems to be too low to warrant its safe administration.[xxvi]
- The principle cardiotonic substance present in leaves of Nerium indicum is Oleandrin which is also the active principle of leaves of N.oleander. Neriodin, Oleanolic acids are also present. The action of neriodin is similar to oleandrin; it is twice as active as Digitoxin. Processes have been patented for the extraction of cardio-active principles from leaves.[xvi].
- "Cardiac Glycosides From Yellow Oleander (Thevetia Peruviana) Seeds"[xxvii]
- "The Cardenolides of Thevetia Peruviana Grown Inn Malaysia"[xxviii]
- "Bio-Chemical and Behavioural Changes in Albino Rats After Treatment With Thevetia Neriifolia Juss. (Yellow Oleander)".[xxix]
- The Toxicity of Yellow Oleander (Thevetia Neriifolia Juss) Seed Kernels To Rats[xxx, xxxi].
- Poisoning From Thevetia Nerifolia (Yellow Oleander)[xxxii,xxxiiixxxiv].
- The Action of Crystalline Thevetin, A Cardiac Glucoside of Thevetia Neriifolia[xxxv]
- Effect of Thevetia Peruviana Seed Cake Based Meal on the Growth, Hematology And Tissues of Rabbits:[xxxvi]
- Comparison of Extraction and TLC Analytic Conditions for Yellow Oleander (Thevetia Peruviana) Root Extract[xxxvii]
- The Antidiarrhoeal, Antimicrobial and Cytotoxic Activities of Ethanol-Extracted

Leaves of Yellow Oleander (Thevetia Peruviana)[xxxviii]

- Fructose-1, 6-Diphosphate (FDP) As A Novel Antidote for Yellow Oleander-Induced Cardiac Toxicity: A Randomized Controlled Double Blind Study[xxxix]
- Effect of Thevetia Peruviana Seed Cake Based Meal on Yhe Growth, Haematology And Tissues of Rabbits[xl]
- "Phytochemical Evaluation and Antispermatogenic Activity of Thevetia Peruviana Methanol Extract in Male Albino Rats."[xli]
- "Anti-Termite and Antimicrobial Properties of Paint Made From Thevetia Peruviana (Pers.) Schum. Oil Extract"[xlii]
- "Additions to The List of Birds Eating The Fruit of Yellow Oleander *(Thevetia Neriifolia)*[xliii]."
- ,"Pharmacokinetics of Digoxin Cross-Reacting Substances In Patients With Acute Yellow Oleander (*Thevetia Peruviana*) Poisoning, Including The Effect of Activated Charcoal"[xliv]
- Anti-Digoxin Fab Fragments In Cardiotoxicity Induced By Ingestion of Yellow Oleander: A Randomised Controlled Trial[xlv]
- "Juvenomimetic Activity of Extracts of Thevetia Neriifolia Juss. To Dysdercus CingulatusF.(Hemiptera:Pyrrhocoreidae) [xlvi]"
- "In Vivo And in Vitro Studies on Thevetia Species Growing in Egypt II. Establishment of in Vitro Tissue Culture System And Production of Cardiac Glycosides"[xlvii];
- "GC/MS Analysis of The Dessert Plants of Apocyanaceae Family: Nerium Oleander L. And Thevetia Peruviana (Pers) Schum"[xlviii] ;
- "Extractability of Thevetia Peruviana Glycosides With Alcohol Mixture"[xlix];
- "Preliminary Phytochemical and Antimicrobial Activity Studies on the Leaves of the Indian Plant *Thevetia Neriifolia Juss*[l]."[li];
- Analysis of Phytochemical Components and Anti-Microbial Activity of the Toxic Plant -Thevetia Peruviana[li]
- *Terminalia chebula* as antidote of *Thevetia neriifolia*[lii]

DISCUSSION

Pita Karavir plant finds its place primarily as cardiac poison. No specific treatment available in modern system of medicine. Several Deaths are being reported from southern parts of India and Shri Lanka for Thevetia Poisoning. Fructose – 1,6-diphosphate is proven antidote against it. Fruit of Terminalia Chebula plant has also been tried as antidote against *Thevetia neriifolia*, which needs further clinical study.

Thevetia neriifolia also finds its place in many *Ayurvedic* preparations, escpecially externally. Purification process also needs to be standerdized so its use in medicines can be assessed for quality purpose.

Special attention should also be given towards its plantation and care as chances of accidental ingestion of plant parts by children are also reported.

CONCLUSION: *Pita Karavir* (*Thevetia neriifolia*) plant is having more importance in Agadtantra. Poisoning incidences are more common in southern parts of India and Sri Lanka. As commonly available, chances of accidental poisoning are more. Its Uses in treatment, cosmetics, as like against stretch marks could open new doors in field. So new insights towards this plant should be developed.

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