Section A-Research paper
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"EXPLORATION OF ANTIDOTE PROPERTIES OF TERMINALIA CHEBULA AGAINST THEVETIA NERIIFOLIA IN ALBINO MICE"

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ABSTRACT

Introduction: *Nerium oleander* and *Thevetia neriifolia* are lethal plants. Poisoning by them is common in tropical and subtropical regions. All parts of these plants are toxic, containing cardiac glycosides. Ingestion causes nausea, vomiting, abdominal pain, diarrhoea, dysrhythmias, and hyperkalemia. Treatment involves activated charcoal and supportive care. Digoxin specific Fab fragments are effective but may be restricted by limited economic resources. **Materials and methods:** *Terminalia chebula* was evaluated against *Thevetia neriifolia* as antidote in Swiss albino mice. Fructose 1, 6 Diphosphate was used as standard antidote.Assessesment was done in terms of physical signs, ECG changes. **Results:** *Terminalia Chebula* significantly increases Time of appearance of tremors (P= 0.024); Time of appearance of RSR (P<0.05); Highly significant in increasing the time of appearance of Paralysis P<0.01); the time of appearance of IRDR (P<0.05); the time of appearance of convulsions (P<0.05); the time of appearance of LORR (P<0.05); the duration of survival period (P<0.05) as compared to control group when administered as antidote against Seed of *Thevetia Neriifolia*. It also significantly increases time of appearance of tremors (P= 0.0143); time of appearance of RSR (P= 0.0196); time duration of appearance of Paralysis (P= 0.0429); significantly increases the time duration of appearance of IRDR RK (P= 0.0196); time of appearance of convulsions (P=0.0196); duration of survival period (P= 0.0455); But not found significantly effective to increase the time of appearance of LORR (P= 0.0619) when administered as antidote against root of *Thevetia Neriifolia.* **Conclusion:** So, This study proposes *Terminalia chebula* for further clinical evaluation of its Antidote properties against *Thevetia neriifolia*

Keywords: *Teminalia chebula; Thevetia neriifolia; Karavir; Haritaki; Prativisha*; Antidote; Cardiac Poison; Nerium; Thevetin;

INTRODUCTION

The yellow oleander Thevetia neriifolia Juss. ex Steud. or Thevetia peruviana Merr. or Thevetia

peruviana Schum. is a commonly found plant in gardens all over India and many other Countries.

It is known with various names all over India as *Karavira(Sanskrita); safed kaner, lal kaner.(Hindi); Shveta karavira, lal karavira.(Bengali);Karavir, Kalhher, Patari, Kanar-tamvadi.(Marathi); Vakana linge, Kangana linge(Kannada);. Kanel chettu.(Tamil); Sumula, Himara dakhali (Arabic); Oleander.(English); Kharajahar(Parasi)*[i]. It grows in and around houses, hutments and on the roadside and is often seen forming protective hedging material around gardens[ii,iii].

Ayurveda has described *Thevetia neriifolia* in detail[iv,v,vi,vii,viii,ix,x,xi,xii,xiii,xiv,xv]. It is categorised under *Hridaya Prabhavak(*Cardiac Poison*).* But various formulations are also described[xvi], in which *Thevetia neriifolia* either used externally or after doing *Shodhana* process. *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.[xvii]

It is a common temple and domestic plant for flowers which are offered to the diety. Children have easy access to this plant in gardens and they may play with and taste the bright yellow flowers and the conspicuous green fruit.

The oleander is an attractive and hardy shrub that thrives in tropical and subtropical regions[xviii]. The common pink oleander, *Nerium oleander*, and the yellow oleander, *Thevetia neriifolia*, are the principle oleander representatives of the family Apocynaceae. Oleanders contain within their tissues cardenolides that are capable of exerting positive inotropic effects on the hearts of animals and humans. The cardiotonic properties of oleanders have been exploited therapeutically and as an instrument of suicide since antiquity. The basis for the physiological action of the oleander cardenolides is similar to that of the classic digitalis glycosides, i.e. inhibition of plasmalemma Na^+, K^+ ATPase. Differences in toxicity and extracardiac effects exist between the oleander and digitalis cardenolides, however. Toxic exposures of humans and wildlife to oleander cardenolides occur with regularity throughout geographic regions where these plants grow.

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[xix,xx] 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.

ECG Changes[xxi] consist of 'P' wave changes which may be in form of absent 'P' waves, or grossly distorted 'P' waves; P-R interval prolongation; ST segment 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 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.

Antidote administration is one of treatment of poisoning. The definition is-"Antidotes are remedies which counteract or neutralize the effect of poison without appreciable harm to body"

The human mortality associated with oleander ingestion is generally very low, even in cases of intentional consumption (suicide attempts). small children and domestic livestock are at increased risk of oleander poisoning.

NEED OF STUDY:

Nerium oleander (common oleander) and *Thevetia neriifolia* (yellow oleander) are potentially lethal plants after ingestion. Poisoning by these plants is a common toxicological emergency in tropical and subtropical parts of the world and intentional self-harm using *T. neriifolia* is prevalent in South Asian countries, especially India and Sri Lanka. All parts of these plants are toxic, and contain a variety of cardiac glycosides including neriifolin, thevetin A[xxii,xxiii] thevetin B[xxiv], and oleandrin[xxv]. Ingestion of

either oleander results in nausea, vomiting, abdominal pain, diarrhoea, dysrhythmias, and hyperkalemia. In most cases, clinical management of poisoning by either *N. oleander* or *T. neriifolia* involves administration of activated charcoal and supportive care. Digoxin specific Fab fragments are an effective treatment of acute intoxication by either species. However, where limited economic resources restrict the use of such Fab fragments, treatment of severely poisoned patients is difficult.

The kernels of the seed is used in suicidal attempts, particularly by young people and especially in northern parts of Shrilanka. Sometimes it is taken in alcoholic drinks[xxvi]. Lot of Researches[xxvii,xxviii] already done on *Thevetia neriifolia*[xxixxxx xxxi,xxxii,xxxiii,xxxiv,xxxv,xxxvi,xxxvii,xxxviii,xxxix] demand invention of Antidote which can be more effective in terms of all things.

Hence, the present study is designed to investigate the action of *Haritaki* (*Terminalia chebula*) as a *Prativisha* (Antidote) of *Karaveera* (*Thevetia neriifolia*) as per reference in *Basavrajiyam* Grantha.

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LACUNA:

Description of *Visha* and its *Prativisha* is seen only in ancient *samhitaas* but much less studies are done, to introduce them in this modern era. *Karavir* (*Thevetia neriifolia)* plant is well known for its cardiotoxicity. The current management of poisoning is not having any specific antidote for it, digoxin specific fab antibody fragment have been used successfully in adult patients but is very costly[xl].

In *Ayurved*, *Haritaki* (*Terminalia chebula*) has been described as *Prativisha* of *Karavir* (*Thevetia neriifolia)* plant, but there is necessity to elaborate this property.

After reviewing literature of *Terminalia chebula* fruit, this remedy seems to be Easily available; Easy to prepare; Easy to administer Easy to carry. So study was planned to evaluate role of *Terminalia chebula* as antidote in *Thevetia neriifolia* poisoning

MATERIALS AND METHODS:

Panchang of *Thevetia neriifolia* was collected from local area of Reshimbaug, Nagpur, Maharashtra and fruit of *Terminalia chebula* was purchased from authentic supplier. Identification and Authentification of samples was done. Authenticated samples were subjected to standardization tests – Total Ash Value; Acid insoluble Ash Value; Aqueous Extractive Value; Alcoholic Extractive Value; Test For Glycosides; Test For Tannins as per Ayurvedic Pharmacopoeia Of India(API) published by CCRAS, alongwith Spectrophotometry (with US-Vis Double Beam Spectrophotometer 6.75 (Sr. No. 2734/1106)); and HPTLC (CAMAG Linomat 5 "Linomat5_170644" S/N 170644; CAMAG TLC "Scanner_171005" S/N 171005 (2.01.02) with CAMAG Visualizer : 171113 (Visualizer_171113)).

Doses were calculated by using toxic dose of *Thevetia neriifolia* and Therapeutic dose of *Terminalia*

chebula conversion factor. Final doses for administration were decided after conducting pilot study as - seed of *Thevetia Neriifolia* 4600mg/kg; root of *Thevetia Neriifolia* - 3500mg/kg; fruit Of *Terminalia chebula* - 780mg/kg; fructose 1,6 diphosphate (FDP) - 0.13mg/kg.

Swiss albino mice (Mus musculus) with avg. weight of 20-30 gms of both sexes were chosen for animal experimentation. All Animals were feeded by supplied food from Nav Maharahtra Chakan oil mills Ltd, Pune and community tape water ad libitum. Room temperature was maintained at 20-24ºC; humidity between 40-60%; Light cycle of 12 Hrs light and 12 Hrs dark. Distilled water and Carboxy methyl Cellulose 5% solution were used as vehicle. Animals were made to fast for 4 hrs before administration of compounds[xli]. All animals were divided in 4 groups, as follows.

Group – I	Only Powdered seed of *Thevetia Neriifolia*	Control Group
Group – II	Powdered seed of *Thevetia Neriifolia* + powdered fruit Of *Teerminalia chebula.*	Experimental Group
Group – III	Powdered root of *Thevetia Neriifolia* + Powdered fruit Of *Terminalia chebula.*	Experimental Group
Group – IV	Powdered seed of *Thevetia Neriifolia* + fructose 1,6 diphosphate (FDP).	Standard Group

The effect of *Terminalia chebula.*as antidote against *Thevetia Neriifolia* was assessed both against Seed and Root. FDP served as standard antidote of *seed* of *Thevetia Neriifolia*. Hence, antidote properties for *Seed* of *Thevetia Neriifolia* were assessed both against control and standard groups. Antidote properties against *Root* of *Thevetia Neriifolia* were assessd against group of animals treated with only *Root of Thevetia Neriifolia* in pilot study(PG).

STATA V10.0 software was used for analysing all the results obtained after doing animal experimental study. To assess effect of *Terminalia chebula.*against seed of *Thevetia Neriifolia* and FDP, Kruskal-Wallis One Way ANOVA Test was applied between Gr I, II and IV, If significant difference of result found then Dunn's multiple comparison test was applied between these groups to assess comparative effect between individual groups.

Efficacy of *Terminalia chebula* against root of *Thevetia Neriifolia* was assessed by applying Wilcoxon ranksum Test (Mann Whitney Test) between Gr III and PG.

Changes in ECG before and after were assessed with help of Signed rank Test.

RESULTS:

1) Standardization Report

a. Standardization Report OF *Thevetia Neriifolia*

TEST	**Reference* Value**	**RESULT**		**REMARKS**
		SEED	*ROOT*	
Foreign Organic Matter(%W/W)	N.A.	0.79	0.81	
Total Ash(%w/w)	6.19%	7.9	6.9	Passes
Acid Insoluble Ash(%w/w)	0.67	0.68	0.86	Passes
Water Soluble Extractives(%w/w)	16.54	23.53	21.18	Passes
Alcohol Soluble Extractives(%w/w)	14.16	22.16	20.39	Passes

b. Standardization Report OF Fruit of *Terminalia chebula.*

TEST	Reference* Value (API)	RESULT	REMARKS
Foreign Organic Matter(%W/W)	Not more than 1%	0.58	Passes
Total Ash(%w/w)	Not more than 5%	3.85	Passes
Acid Insoluble Ash(%w/w)	Not more than 5%	1.35	Passes
Water Soluble Extractives(%w/w)	Not less than 60%	65.17	Passes
Alcohol Soluble Extractives(%w/w)	Not less than 40%	42.12	Passes

c. Standardization Report OF Extract of *Terminalia chebula*

TEST	RESULT
Specific Gravity at 25^0C	1.0097
pH (Directly of extract)	3.33
Dynamic Viscosity (mPs)	24.50
Total Solids (w/v)	0.2817

2) HPTLC Report

HPTLC Report				
No.	**Sample**	**254nm**	**366nm**	**600nm**
1.	SEED OF *Thevetia neriifolia*	0.13;0.29; 0.96; 0.82; 0.88; 1.12; 0.71; 1.08; 0.43; 0.91; 0.48; 0.35; 0.39	0.12; 0.41; 0.94; 0.78; 0.90; 1.08; 0.71; 0.49; 0.15; 0.91; 0.48; 0.35; 0.39	0.69; 0.69; 0.99; 0.96; 0.79; 0.87; 0.04; 0.07; 0.23; 0.43; 0.48; 0.17; 0.16; 0.28; 0.38; 1.09; 0.08; 1.15
2.	ROOT OF *Thevetia neriifolia*	0.08; 0.28; 1.01; 0.92; 0.78; 0.58	0.08; 0.91; 1.01; 0.92; 0.78; 0.58	0.56; 0.16; 1.03; 0.92; 0.89; 0.80; 0.65; 1.13; 0.23; 0.73; 0.28; 1.16; 0.47
3.	FRUIT OF *Terminalia chebula*	0.08; 0.31; 0.98; 0.90; 0.83; 0.78; 0.68; 0.44; 0.63; 0.51	0.51; 0.54; 0.98; 0.92; 0.80; 0.68; 0.68; 0.44; 0.63; 0.51	1.11; 0.03
4.	EXTRACT OF *Terminalia chebula*	0.90; 0.03	0.90; 0.03	0.90; 0.03

a. HPTLC of Seed of seed of *Thevetia Neriifolia*

On analyzing under scanner at 254 nm, the chromatogram showed 13 peaks, while at 366 nm also the chromatogram showed 13 peaks but with appearance of some new substances. And after

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derivatization the chromatogram showed 18 peaks. Spots of Rf 0.96 & 0.43 at 254nm disappeared at 366nm reappeared after derivatization.

b. HPTLC of Seed of Root of *Thevetia Neriifolia*

On analyzing under scanner at 254 nm, the chromatogram showed 6 peaks, while at 366 nm also the chromatogram showed same 6 peaks. And after derivatization the chromatogram showed 13 peaks. All the spots at 254nm & 366nm were all the same. Except spot of Rf 0.92 all the apots disappeared after derivatization.

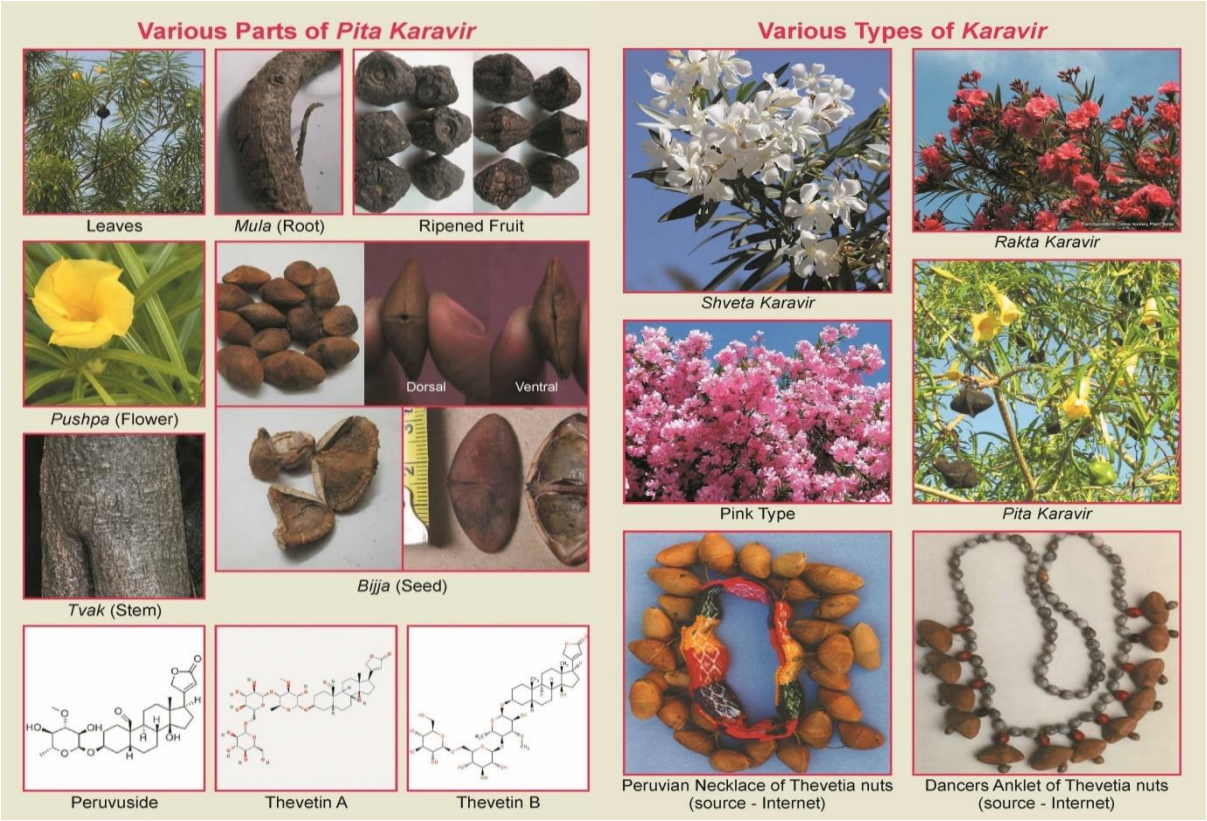
c. HPTLC of Seed of Fruit of *Terminalia chebula.*

On analyzing under scanner at 254 nm, the chromatogram showed 10 peaks, while at 366 nm also the chromatogram showed 10 peaks but with appearance of some new substances.. All the spots at 254nm & 366nm disappeared and new spot at Rf 0.03 was appeared after derivatization.

d. HPTLC of Seed of Extract of *Terminalia chebula*

On analyzing under scanner at 254 nm and 366nm, the chromatogram showed same 2 peaks. same spots remained after derivatization also.


Experimental Study
Suspension of Drugs
Oral Feeding
Observation of Symptions
Anaesthesia
Recording BP
Recording ECG
Haritaki
Plant of Haritaki
Fruit of Haritaki
FDP
Fructose 1-6 oiphorphte
Chemical Structure


Various Parts of Pita Karavir
Leaves
Mula (Root)
Ripened Fruit
Pushpa (Flower)
Dorsal
Ventral
Tvak (Stem)
Bijja (Seed)
Peruvuside
Thevetin A
Thevetin B
Various Types of Karavir
Shveta Karavir
Rakta Karavir
Pink Type
Pita Karavir
Peruvian Necklace of Thevetia nuts (source - Internet)
Dancers Anklet of Thevetia nuts (source - Internet)

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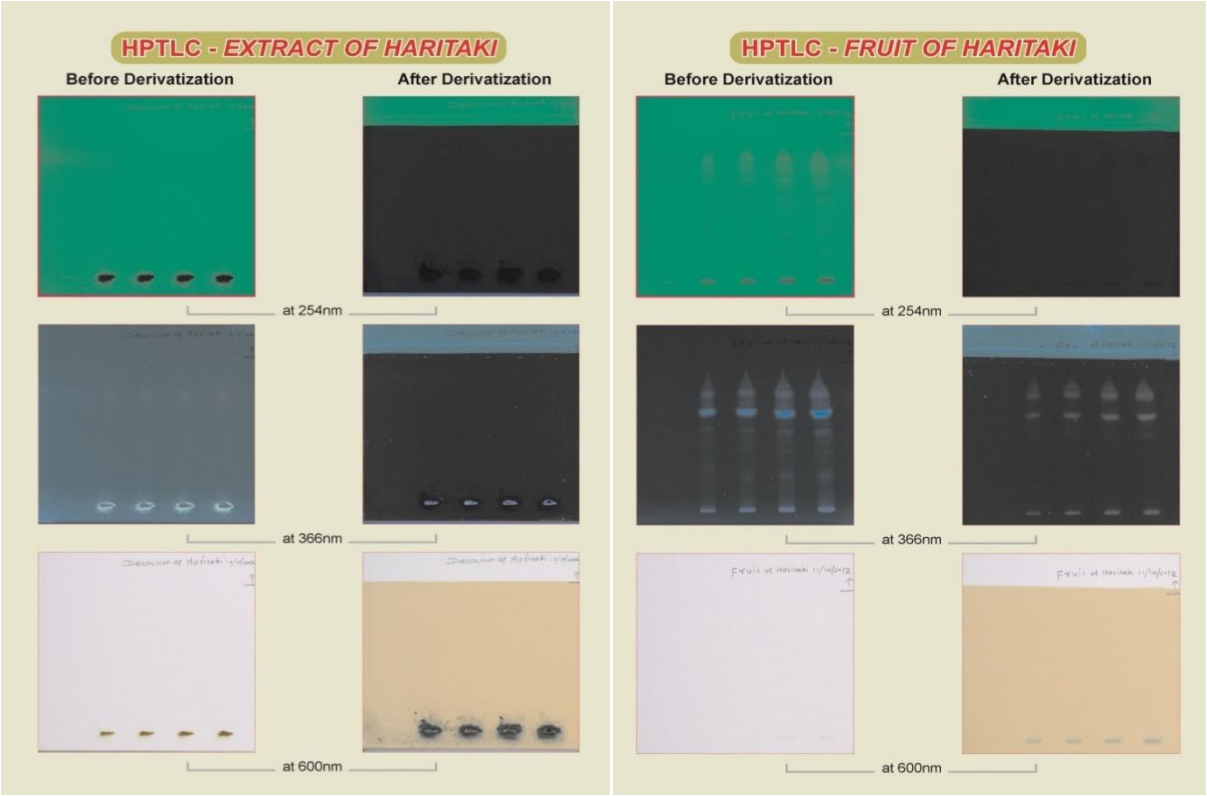
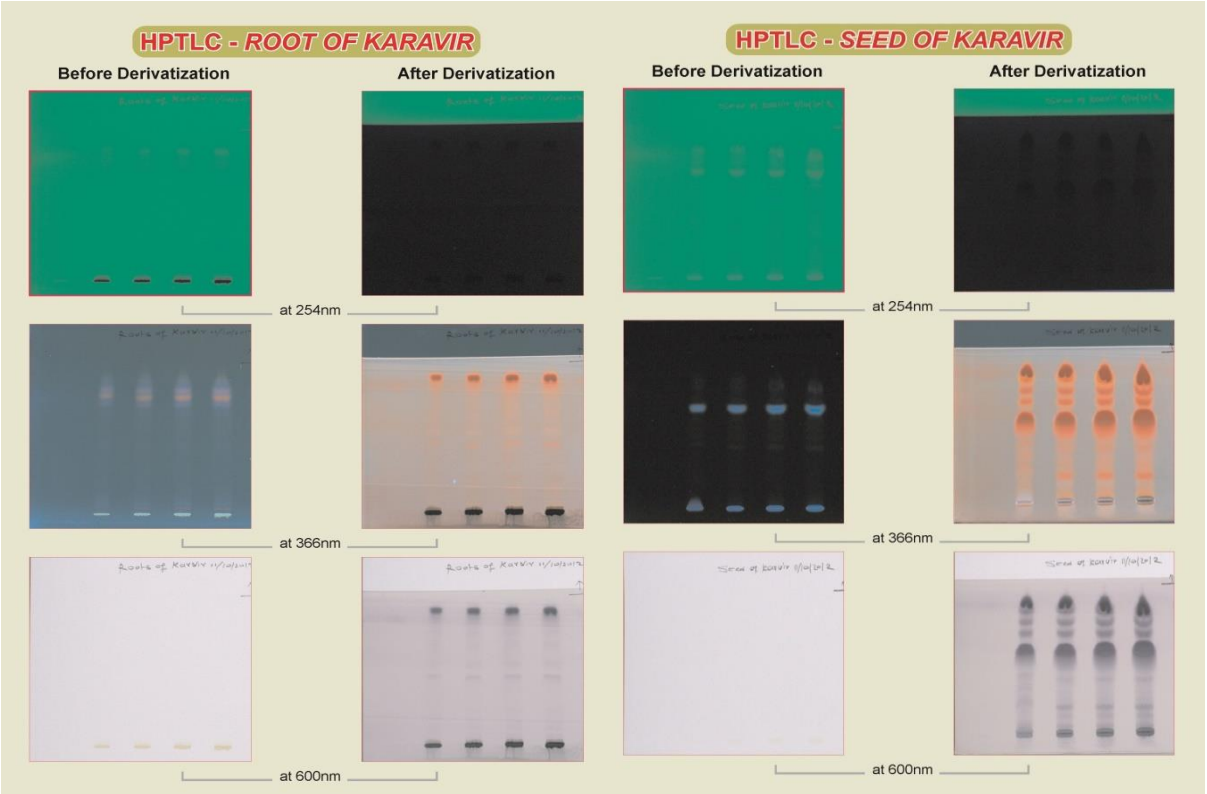




1) Results of Animal Study

TABLE NO. 1: APPEARANCE OF TREMOURS					
	GROUP1	GROUP2	GROUP3	GROUP4	PG
MEAN	10.5	19.5	26.67	22.83	9.67
SD	0.83	7.17	2.58	5.11	0.57
MEDIAN	10	18.5	25	23.5	10
Comparison Between Gr I, II & IV(Kruskal-Wallis Test)					
KW Statistics=9.64			P=0.0081 , HS		
Dunn's Multiple Comparison Test					
Comparison		Mean Rank Difference		P Value	
Gr1 Vs Gr2		7.91		P=0.024, S	
Gr1 Vs Gr4		10.75		P=0.002, HS	
Gr2 Vs Gr4		2.83		P=0.829,NS	
Comparison of Gr3 with PG(Wilcoxon ranksum Test)					
Z = 2.449			P = 0.0143, S		

TABLE NO. 2: APPEARANCE OF RAPID & SHALLOW RESPIRATION(RSR)					
	GROUP1	GROUP2	GROUP3	GROUP4	PG
MEAN	33	45.83	46.67	41.67	15
SD	2.45	3.76	12.52	11.25	3
MEDIAN	34	45	47.5	42.5	15
Comparison Between Gr I, II & IV(Kruskal-Wallis Test)					
KW Statistics = 7.765			P = 0.0147, S		
Dunn's Multiple Comparison Test					
Comparison		Mean Rank Difference		P Value	
Gr1 Vs Gr2		8.417		P < 0.05, S	
Gr1 Vs Gr4		4.583		P > 0.05, NS	
Gr2 Vs Gr4		3.833		P > 0.05, NS	

Comparison of Gr3 with PG(Wilcoxon ranksum Test)	
Z = 2.334	P = 0.0196, S

TABLE NO. 3: APPEARANCE OF PARALYSIS					
	GROUP1	GROUP2	GROUP3	GROUP4	PG
MEAN	62.5	110	114.16	108	65
SD	15.08	12.24	35.83	12.55	7.07
MEDIAN	65	112.5	105	105	65
Comparison Between Gr I, II & IV(Kruskal-Wallis Test)					
KW Statistics= 13.33			P = 0.0040, HS		
Dunn's Multiple Comparison Test					

Comparison	Mean Rank Difference	P Value
Gr1 Vs Gr2	12.08	P < 0.01, HS
Gr1 Vs Gr4	11.4	P < 0.05, S
Gr2 Vs Gr4	0.6833	P > 0.05, NS
Comparison of Gr3 with PG(Wilcoxon ranksum Test)		
Z = 2.024		P = 0.0429, S

TABLE NO. 4: APPEARANCE OF INCREASED RATE & DEPTH OF RESPIRATION(IRDR)					
	GROUP1	GROUP2	GROUP3	GROUP4	PG
MEAN	90.83	157.5	132.5	103	38.33
SD	15.63	38.82	30.62	29.92	24.66
MEDIAN	95	165	127.5	90	50
Comparison Between Gr I, II & IV(Kruskal-Wallis Test)					
KW Statistics = 8.281			P= 0.0088, HS		
Dunn's Multiple Comparison Test					
Comparison		Mean Rank Difference		P Value	
Gr1 Vs Gr2		8.00		P < 0.05, S	

ISSN 2063-5346

Gr1 Vs Gr4	1.733	P > 0.05, NS
Gr2 Vs Gr4	6.267	P > 0.05, NS
Comparison of Gr3 with PG(Wilcoxon ranksum Test)		
Z = 2.334	P = 0.0196, S	

TABLE NO. 5: APPEARANCE OF CONVULSIONS

	GROUP1	GROUP2	GROUP3	GROUP4	PG
MEAN	135.83	189	180	144	61.66
SD	9.7	20.12	34.2	41.59	44.81
MEDIAN	135	180	187.5	140	85
Comparison Between Gr I, II & IV(Kruskal-Wallis Test)					
KW Statistics = 8.61			P = 0.0350, S		
Dunn's Multiple Comparison Test					
Comparison		Mean Rank Difference		P Value	
Gr1 Vs Gr2		9.72		P < 0.05, S	
Gr1 Vs Gr4		2.21		P > 0.05, NS	
Gr2 Vs Gr4		7.5		P > 0.05, NS	
Comparison of Gr3 with PG(Wilcoxon ranksum Test)					
Z = 2.334			P = 0.0196, S		

TABLE NO. 6: APPEARANCE OF LORR

	GROUP1	GROUP2	GROUP3	GROUP4	PG
MEAN	140	150	142.5	158	87.5
SD	6.32	31.82	38.82	32.9	3.53
MEDIAN	137.5	150	142.5	145	87.5
Comparison Between Gr I, II & IV(Kruskal-Wallis Test)					
KW Statistics = 10.01			P= 0.0015, HS		
Dunn's Multiple Comparison Test					
Comparison		Mean Rank Difference		P Value	
Gr1 Vs Gr2		7.933		P < 0.05, S	

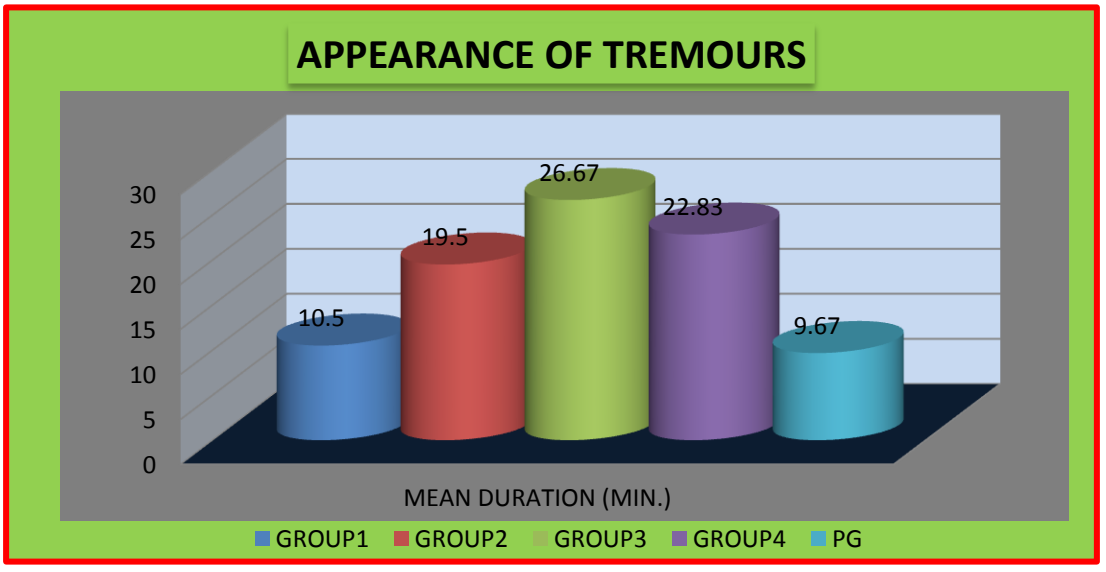
ISSN 2063-5346

Gr1 Vs Gr4	7.533	P < 0.05, S
Gr2 Vs Gr4	0.4000	P > 0.05, NS
Comparison of Gr3 with PG(Wilcoxon ranksum Test)		
Z = 1.867	P = 0.0619, NS	

TABLE NO. 7: APPEARANCE OF DEATH

	GROUP1	GROUP2	GROUP3	GROUP4	PG
MEAN	165	228	248.33	185	62.5
SD	10	22.8	70.89	31.45	67.17
MEDIAN	165	225	242.5	175	62.5

Comparison Between Gr I, II & IV(Kruskal-Wallis Test)		
KW Statistics = 8.281	P = 0.0159, S	
Dunn's Multiple Comparison Test		
Comparison	Mean Rank Difference	P Value
Gr1 Vs Gr2	9.21	P < 0.05, S
Gr1 Vs Gr4	2.91	P > 0.05, NS
Gr2 Vs Gr4	6.3	P < 0.05, S
Comparison of Gr3 with PG(Wilcoxon ranksum Test)		
Z = 2	P = 0.0455, S	



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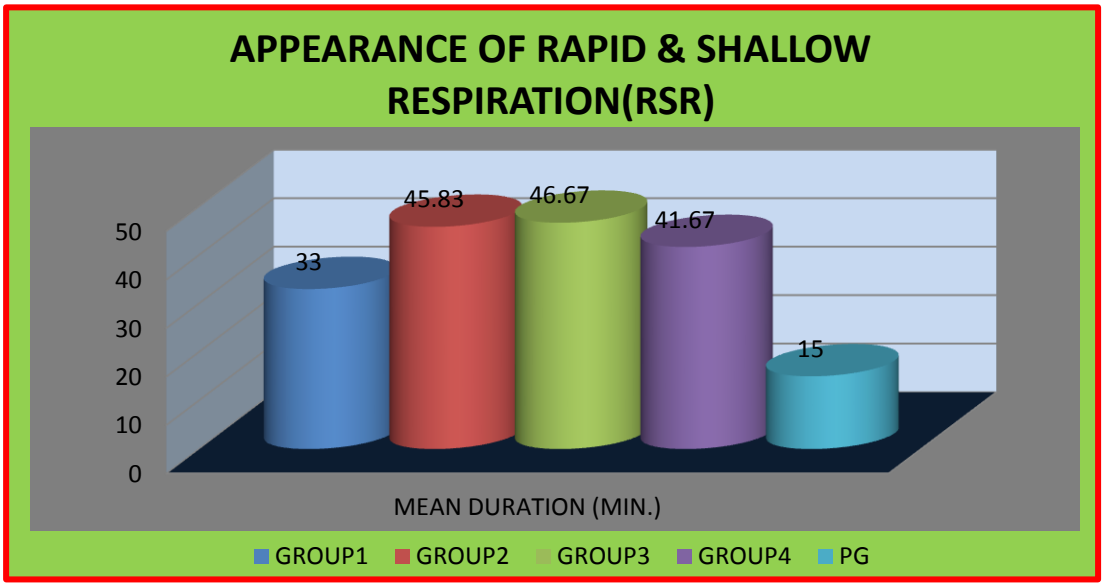
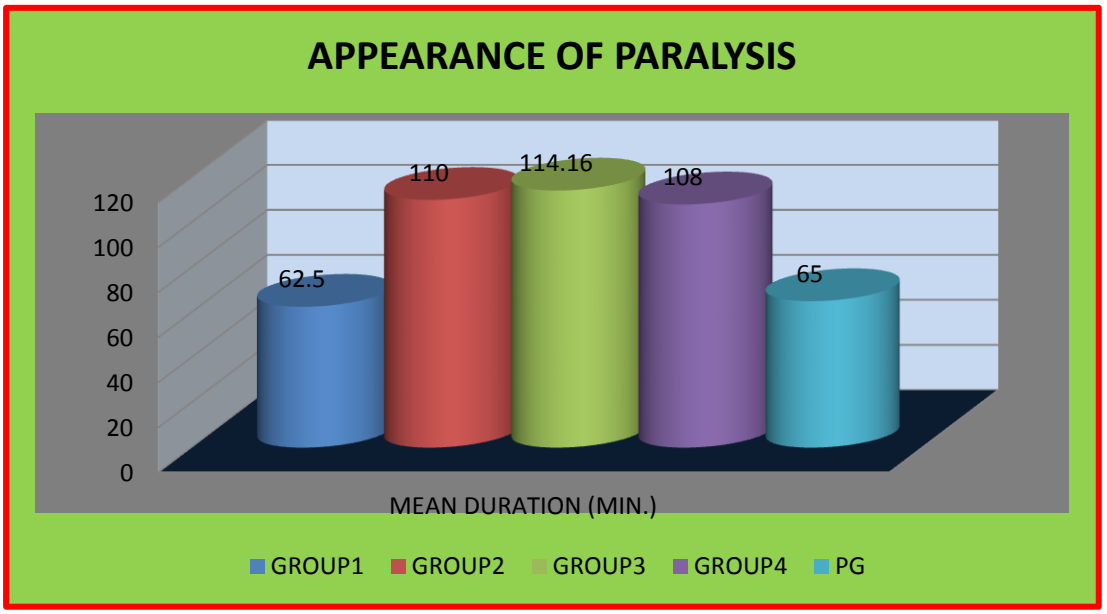
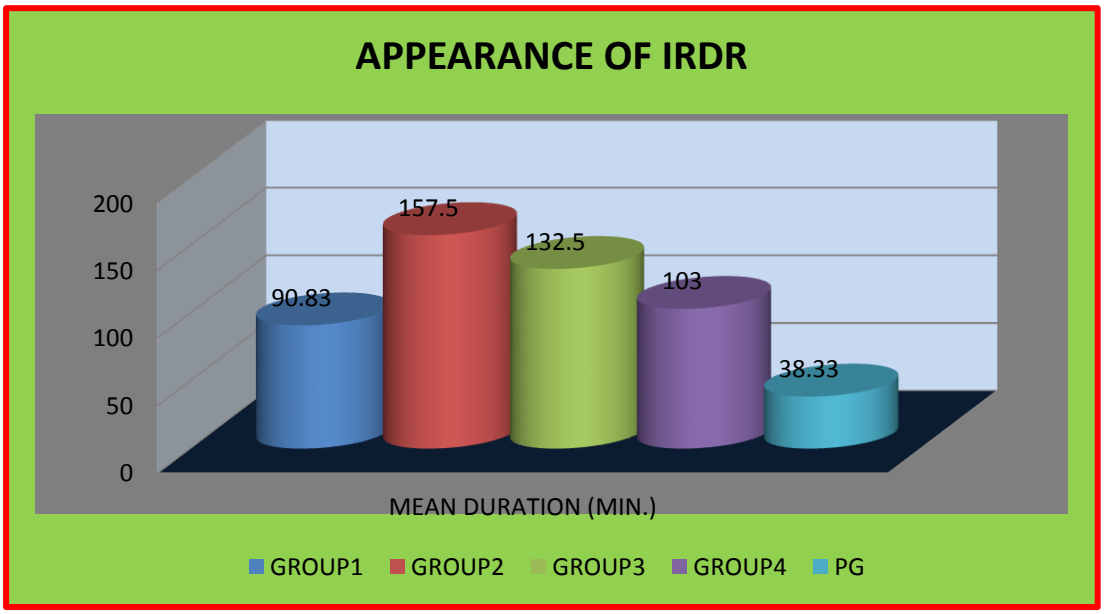
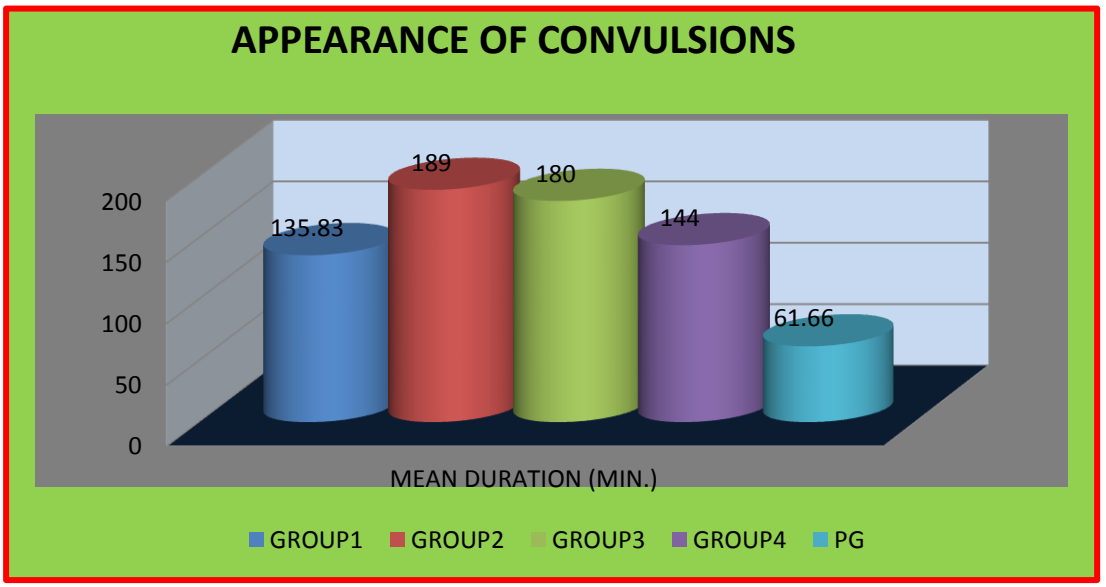
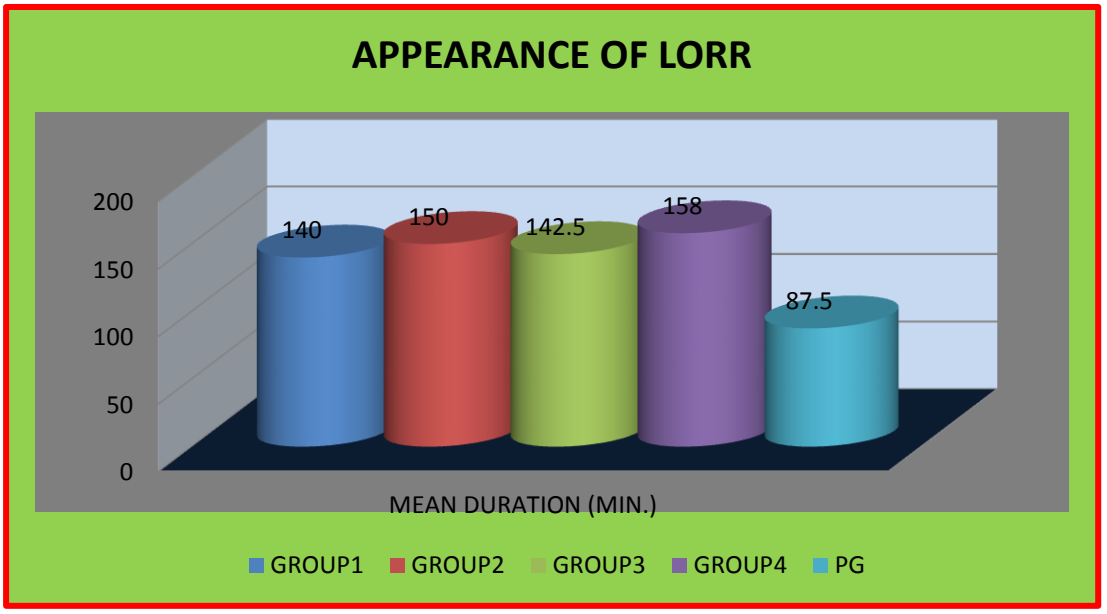
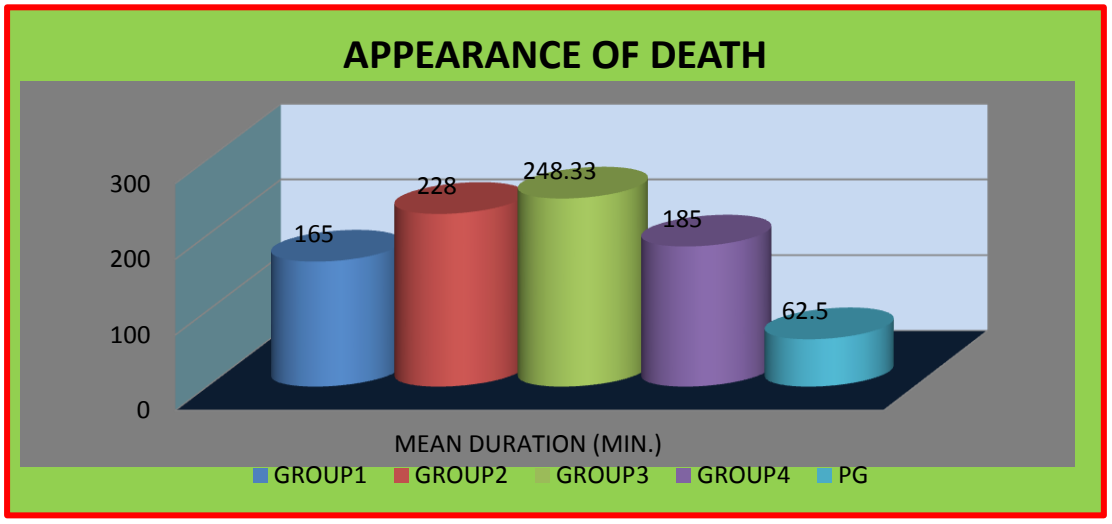




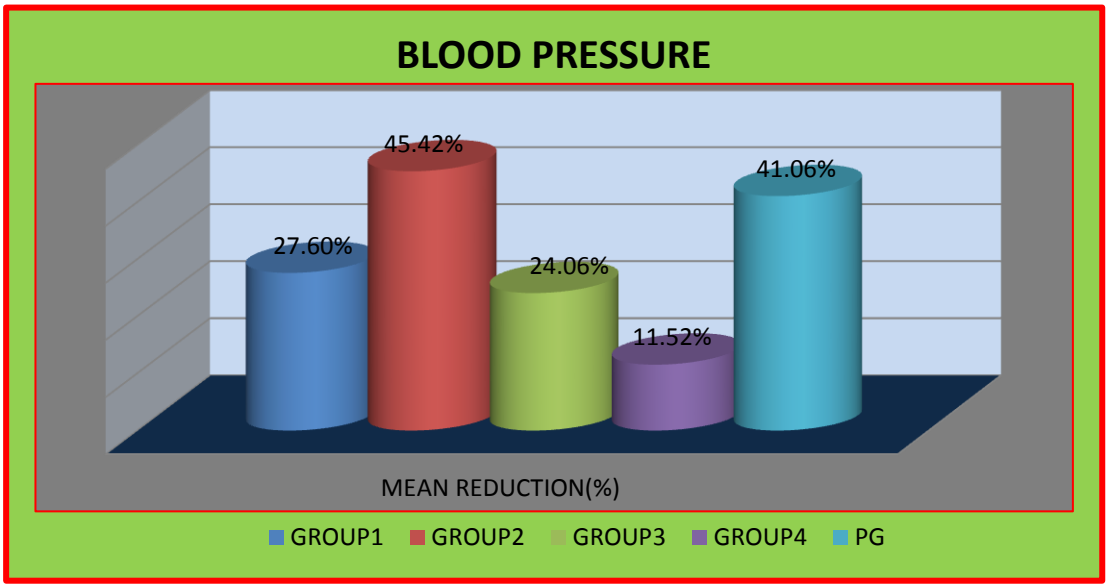


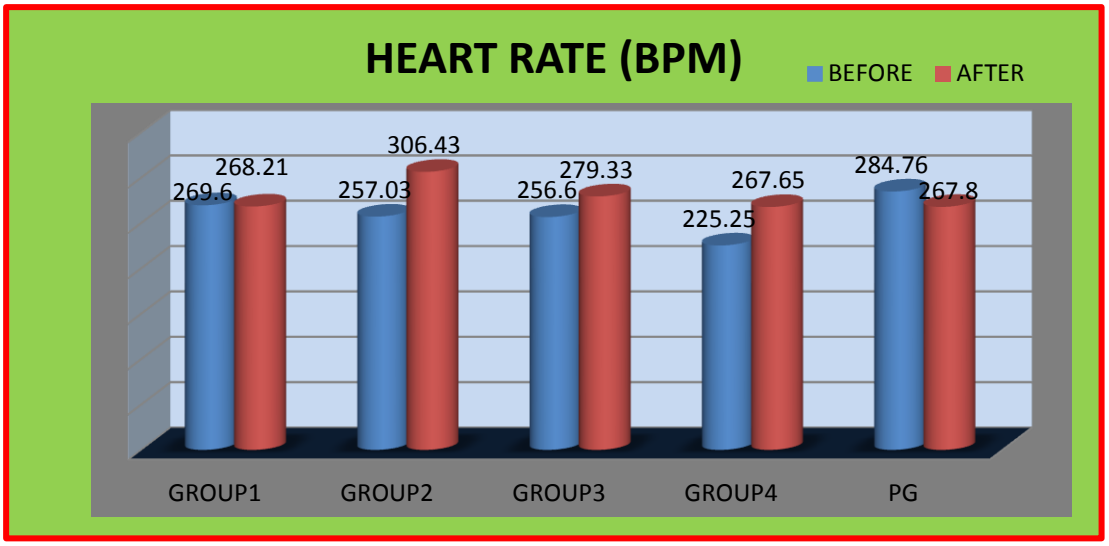

APPEARANCE OF CONVULSIONS
200
150
100
50
0
135.83
189
180
144
61.66
MEAN DURATION (MIN.)
GROUP1
GROUP2
GROUP3
GROUP4
PG

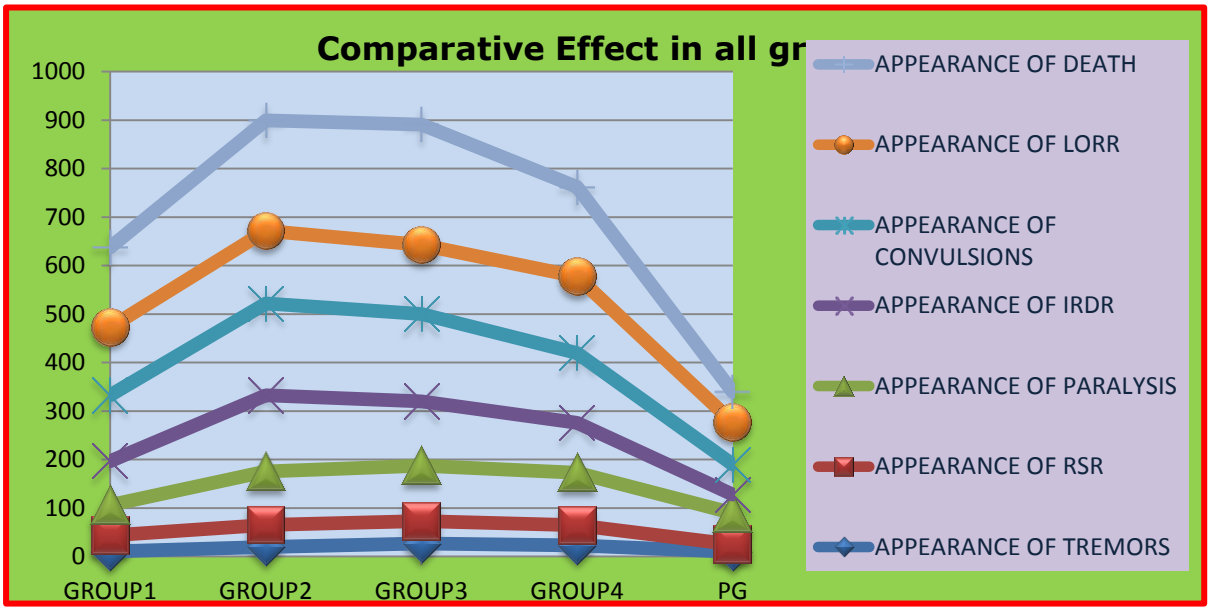

APPEARANCE OF LORR
200
150
100
50
0
140
150
142.5
158
87.5
MEAN DURATION (MIN.)
GROUP1
GROUP2
GROUP3
GROUP4
PG


APPEARANCE OF DEATH
300
200
100
0
165
228
248.33
185
62.5
MEAN DURATION (MIN.)
GROUP1
GROUP2
GROUP3
GROUP4
PG

ISSN 2063-5346







❖ ECG ANALYSIS

TABLE NO. 8: CHANGES IN HEART RATE (BPM)					
		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	269.6	80.58	281.35	Z=0.105
	AFTER	268.21	41.07	272.85	P=0.9165, NS
GROUP2	BEFORE	257.03	525.23	252.73	Z=1.992
	AFTER	306.43	53.01	330.4	P=0.0464,S
GROUP3	BEFORE	256.6	56.86	238.15	Z=0.641
	AFTER	279.33	89.90	323.25	P=0.5218,NS
GROUP4	BEFORE	225.25	35.72	224.75	Z=1.121
	AFTER	267.65	98.05	299.9	P=0.2623,NS
PG	BEFORE	284.76	26.14	288.9	Z=0.655
	AFTER	267.8	60.68	254.3	P=0.5127,NS

TABLE NO. 9: CHANGES IN BLOOD PRESSURE						
		MEAN	S.D.	MEDIAN		REDUCTION(%)
GROUP1	BEFORE	97.83	14.59	101	Z=1.363	27.6%
	AFTER	70.83	40.60	74	P=0.1730, NS	
GROUP2	BEFORE	105.16	19.87	108.5	Z= 1.782	45.42%
	AFTER	57.4	48.23	52	P= 0.0747,NS	
GROUP3	BEFORE	98.83	21.70	102	Z=0.943	24.06%
	AFTER	74.67	52.54	63	P=0.3454, NS	
GROUP4	BEFORE	92	21.73	91.5	Z=1.905	11.52%
	AFTER	81.4	34.08	91.5	P=0.0568, NS	
PG	BEFORE	108	3.46	106	Z=1.604	41.06%
	AFTER	63.66	15.69	69	P=0.1088, NS	

TABLE NO. 10: CHANGES IN RR INTERVAL(S)					
		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.23	0.04	0.22	Z=0.314
	AFTER	0.26	0.12	0.21	P=0.7532, NS

GROUP2	BEFORE	0.24	0.04	0.24	Z=1.992
	AFTER	0.21	0.04	0.19	P=0.0464, S
GROUP3	BEFORE	0.24	0.05	0.25	Z=0.6310
	AFTER	0.25	0.10	0.20	P=0.6753,NS
GROUP4	BEFORE	0.27	0.04	0.27	Z=1.281
	AFTER	0.30	0.23	0.20	P=0.2002,NS
PG	BEFORE	0.21	0.04	0.21	Z=0.218
	AFTER	0.23	0.05	0.23	P=0.8273,NS

TABLE NO. 11: CHANGES IN PR INTERVAL(S)

		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.038	0.004	0.039	Z=2.023
	AFTER	0.05	0.007	0.049	P=0.0431, S
GROUP2	BEFORE	0.043	0.004	0.04	Z=0.994
	AFTER	0.04	0.003	0.04	P=0.3452, NS
GROUP3	BEFORE	0.04	0.01	0.04	Z=0.320
	AFTER	0.04	0.009	0.04	P=0.7488, NS
GROUP4	BEFORE	0.04	0.007	0.04	Z=0.160
	AFTER	0.04	0.007	0.04	P=0.8728,NS
PG	BEFORE	0.03	0.0036	0.03	Z=1.964
	AFTER	0.055	0.005	0.05	P=0.0495, S

TABLE NO. 12: CHANGES IN P DURATION(S)

		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.025	0.005	0.023	Z=2.201
	AFTER	0.016	0.004	0.014	P=0.0277, S
GROUP2	BEFORE	0.022	0.0063	0.02	Z=0.447
	AFTER	0.016	0.006	0.016	P=0.6547, NS
GROUP3	BEFORE	0.018	0.002	0.019	Z=1.922
	AFTER	0.013	0.005	0.01	P=0.0547,NS

GROUP4	BEFORE	0.02	0.004	0.02	Z=0.961
	AFTER	0.017	0.01	0.01	P=0.3367,NS
PG	BEFORE	0.017	0.005	0.01	Z=1.528
	AFTER	0.028	0.007	0.03	P=0.1266,NS

TABLE NO. 13: CHANGES IN QRS INTERVAL(S)

		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.02	0.009	0.015	Z=2.20
	AFTER	0.009	0.001	0.009	P=0.0277, S
GROUP2	BEFORE	0.01	0.0007	0.01	Z=1.782
	AFTER	0.013	0.003	0.012	P=0.0747, NS
GROUP3	BEFORE	0.011	0.002	0.01	Z=2.562
	AFTER	0.014	0.001	0.014	P=0.0104, NS
GROUP4	BEFORE	0.009	0.001	0.0099	Z=1.826
	AFTER	0.012	0.002	0.012	P=0.0679, NS
PG	BEFORE	0.01	0.002	0.009	Z=1.964
	AFTER	0.015	0.001	0.015	P=0.0495, S

TABLE NO. 14: CHANGES IN QT INTERVAL(S)

		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.047	0.016	0.04	Z=2.20
	AFTER	0.026	0.001	0.027	P=0.0277, S
GROUP2	BEFORE	0.028	0.004	0.027	Z=0.105
	AFTER	0.027	0.008	0.002	P=0.9165, NS
GROUP3	BEFORE	0.03	0.004	0.03	Z=0.800
	AFTER	0.033	0.012	0.03	P=1.000, NS
GROUP4	BEFORE	0.029	0.003	0.028	Z=0.913
	AFTER	0.028	0.01	0.026	P=0.3613, NS
PG	BEFORE	0.026	0.001	0.026	Z=1.964
	AFTER	0.04	0.003	0.04	P=0.495, S

ISSN 2063-5346

TABLE NO. 15: CHANGES IN QTc (S)					
		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.095	0.018	0.09	Z=2.20
	AFTER	0.056	0.004	0.057	P=0.0277, S
GROUP2	BEFORE	0.058	0.009	0.058	Z=0.314
	AFTER	0.057	0.013	0.05	P=0.7532, NS
GROUP3	BEFORE	0.063	0.013	0.06	Z=0.801
	AFTER	0.068	0.013	0.07	P=0.4233, NS
GROUP4	BEFORE	0.057	0.01	0.05	Z=0.548
	AFTER	0.06	0.019	0.06	P=0.5839, NS
PG	BEFORE	0.058	0.002	0.058	Z=1.964
	AFTER	0.08	0.017	0.08	P=0.0495, S

TABLE NO. 16: CHANGES IN JT INTERVAL (S)					
		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.0274	0.01	0.024	Z=2.20
	AFTER	0.017	0.002	0.017	P=0.0277, S
GROUP2	BEFORE	0.018	0.0049	0.0169	Z=0.973
	AFTER	0.0129	0.007	0.012	P=0.34541,NS
GROUP3	BEFORE	0.019	0.0027	0.02	Z=0.961
	AFTER	0.018	0.012	0.01	P=0.3367, NS
GROUP4	BEFORE	0.196	0.002	0.019	Z=0.730
	AFTER	0.015	0.009	0.01	P=0.4652, NS
PG	BEFORE	0.016	0.004	0.017	Z=1.528
	AFTER	0.025	0.004	0.02	P=0.1266, NS

TABLE NO. 17: CHANGES IN TPEAK TEND INTERVAL (S)					
		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.0184	0.006	0.017	Z=1.992
	AFTER	0.011	0.002	0.012	P=0.0464, S

ISSN 2063-5346

GROUP2	BEFORE	0.0127	0.003	0.012	Z=1.153
	AFTER	0.0078	0.006	0.006	P=0.2489, NS
GROUP3	BEFORE	0.013	0.002	0.013	Z=0.961
	AFTER	0.011	0.009	0.008	P=0.3367. NS
GROUP4	BEFORE	0.013	0.002	0.013	Z=0.913
	AFTER	0.008	0.007	0.004	P=0.3613, NS
PG	BEFORE	0.01	0.003	0.01	Z=1.964
	AFTER	0.017	0.0026	0.019	P=0.0495, S

TABLE NO. 18: CHANGES IN P AMPLITUDE (mV)

		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.084	0.05	0.093	Z=0.135
	AFTER	0.08	0.03	0.085	P=0.8927, NS
GROUP2	BEFORE	0.117	0.057	0.10	Z=2.023
	AFTER	0.0189	0.04	0.00005	P=0.0431, S
GROUP3	BEFORE	0.10	0.015	0.10	Z=2.882
	AFTER	-0.009	0.056	-0.0006	P=0.0039, HS
GROUP4	BEFORE	0.13	0.05	0.13	Z=1.922
	AFTER	0.04	0.066	0.0002	P=0.0547, NS
PG	BEFORE	0.106	0.017	0.11	Z=0.218
	AFTER	0.11	0.018	0.019	P=0.8273, NS

TABLE NO. 19: CHANGES IN Q AMPLITUDE (mV)

		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.005	0.02	0.004	Z=0.524
	AFTER	-0.015	0.033	0.086	P=0.6002, NS
GROUP2	BEFORE	0.0189	0.013	0.02	Z=0.734
	AFTER	0.03	0.07	-0.0004	P=0.4631, NS
GROUP3	BEFORE	-0.006	0.039	0.01	Z=0.320
	AFTER	-0.043	0.13	-0.0003	P=0.7488, NS

GROUP4	BEFORE	0.027	0.047	0.009	Z=0.320
	AFTER	0.02	0.03	0.01	P=0.7488, NS
PG	BEFORE	-0.017	0.04	0.008	Z=1.091
	AFTER	0.012	0.028	0.023	P=0.2752, NS

TABLE NO. 20: CHANGES IN R AMPLITUDE (mV)

		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.66	0.35	0.60	Z=0.105
	AFTER	0.73	0.45	0.56	P=0.9165, NS
GROUP2	BEFORE	1.14	0.34	1.07	Z=2.201
	AFTER	0.32	0.53	0.009	P=0.0277, S
GROUP3	BEFORE	0.89	0.43	0.85	Z=1.44
	AFTER	0.47	0.65	0.12	P=0.1495, NS
GROUP4	BEFORE	1.41	0.49	1.52	Z=2.242
	AFTER	0.48	0.66	0.15	P=0.0250, S
PG	BEFORE	0.928	0.62	0.74	Z=0.218
	AFTER	0.82	0.38	0.65	P=0.8273, NS

TABLE NO. 21: CHANGES IN S AMPLITUDE (mV)

		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	-0.30	0.12	-0.34	Z=1.78
	AFTER	-0.19	0.13	-0.24	P=0.0747, NS
GROUP2	BEFORE	-0.26	0.16	-0.26	Z=1.992
	AFTER	-0.079	0.13	-0.0007	P=0.0464, S
GROUP3	BEFORE	-0.23	0.26	-0.15	Z=1.922
	AFTER	-0.068	0.12	-0.01	P=0.0547, NS
GROUP4	BEFORE	0.16	0.23	0.09	Z=1.278
	AFTER	0.041	0.20	0.0002	P=0.2012, NS
PG	BEFORE	-0.21	0.17	-0.23	Z=1.604
	AFTER	-0.37	0.03	-0.38	P=0.1088, NS

TABLE NO. 22: CHANGES IN ST HEIGHT (mV)					
		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.38	0.16	0.33	Z=2.201
	AFTER	0.11	0.18	0.13	P=0.0277, S
GROUP2	BEFORE	0.37	0.10	0.35	Z=2.201
	AFTER	0.07	0.16	0.003	P=0.0277, S
GROUP3	BEFORE	0.34	0.17	0.29	Z=1.281
	AFTER	0.137	0.35	-0.0001	P=0.2002, NS
GROUP4	BEFORE	0.43	0.16	0.45	Z=2.242
	AFTER	0.13	0.17	0.09	P=0.0250,S
PG	BEFORE	0.29	0.27	0.17	Z=0.535
	AFTER	0.33	0.06	0.33	P=0.5930, NS

TABLE NO. 23: CHANGES IN T AMPLITUDE (mV)					
		MEAN	S.D.	MEDIAN	
GROUP1	BEFORE	0.28	0.21	0.32	Z=0.314
	AFTER	0.31	0.21	0.22	P=0.07532, NS
GROUP2	BEFORE	0.488	0.148	0.47	Z=2.201
	AFTER	0.14	0.21	0.005	P=0.0277, S
GROUP3	BEFORE	0.37	0.18	0.32	Z=0.961
	AFTER	0.27	0.36	0.10	P=0.3367, NS
GROUP4	BEFORE	0.48	0.18	0.51	Z=1.826
	AFTER	0.17	0.23	0.0002	P=0.0679, NS
PG	BEFORE	0.33	0.31	0.18	Z=0.000
	AFTER	0.34	0.04	0.35	P=1.0000, NS

ISSN 2063-5346

TABLE NO. 24: comparison of changes in ECG between Group I, II & IV (By using Kruskal-Wallis Test)

No.	Variable	Kruskal-Wallis statistics X^2=	Probability
1	Blood Pressure	0.363	P=0.8342, NS
2	RR Interval (s)	0.222	P=0.8948, NS
3	Heart Rate (BPM)	0.635	P=0.7281, NS
4	PR Interval (s)	5.593	P=0.0610, NS
5	P Duration (s)	1.638	P=0.497, NS
6	QRS Interval (s)	5.881	P=0.0528, NS
7	QT Interval (s)	8.820	P=0.0120, S
8	QTc (s)	5.155	P=0.0760, NS
9	JT Interval (s)	7.927	P=0.0190, S
10	Tpeak Tend Interval (s)	9.38	P=0.0092, HS
11	P Amplitude (mV)	4.547	P=0.1029, NS
12	Q Amplitude (mV)	1.135	P=0.5617, NS
13	R Amplitude (mV)	5.977	P=0.0504, NS
14	S Amplitude (mV)	6.319	P=0.0424, S
15	ST Height (mV)	0.0818	P=0.9721, NS
16	T Amplitude (mV)	4.014	P=0.1344, NS

TABLE NO. 25: Dunn's Multiple Comparison Test for ECG changes between Gr I,II & IV

Dunn's Multiple Comparison Test for QT Interval		
Comparison	Mean Rank Difference(Z)	P Value
Gr1 Vs Gr2	2.402	0.0163,S
Gr1 Vs Gr4	0.0000	1.000,NS
Gr2 Vs Gr4	2.556	0.0106,S
Dunn's Multiple Comparison Test for JT Interval		

Comparison	Mean Rank Difference(Z)	P Value
Gr1 Vs Gr2	2.402	0.0703,NS
Gr1 Vs Gr4	0.183	0.8551,NS
Gr2 Vs Gr4	2.373	0.0176,S
Dunn's Multiple Comparison Test for T peak Tend Interval		
Comparison	Mean Rank Difference(Z)	P Value
Gr1 Vs Gr2	2.562	0.0104,S
Gr1 Vs Gr4	0.183	0.8551,NS
Gr2 Vs Gr4	2.373	0.0176,S
Dunn's Multiple Comparison Test for S amplitude		
Comparison	Mean Rank Difference(Z)	P Value
Gr1 Vs Gr2	2.562	0.0104,S
Gr1 Vs Gr4	0.548	0.5839,NS
Gr2 Vs Gr4	1.643	0.1003,NS

TABLE NO. 26: comparison of changes in ECG between Group III & Pilot study animals.(By using Signed rank test)

No.	Variable	Z=	Probability
1	Blood Pressure	Z=0.516	P=0.6056, NS
2	RR Interval (s)	Z=0.218	P=0.8273, NS
3	Heart Rate (BPM)	Z=0.655	P=0.5127, NS
4	PR Interval (s)	Z=1.964	P=0.0495,S
5	P Duration (s)	Z=1.528	P=0.1266, NS
6	QRS Interval (s)	Z=1.964	P=0.0495, S
7	QT Interval (s)	Z=1.964	P=0.0495, S
8	QTc (s)	Z=1.964	P=0.0495, S
9	JT Interval (s)	Z=1.528	P=0.1266, NS
10	Tpeak Tend Interval (s)	Z=1.964	P=0.0495, S
11	P Amplitude (mV)	Z=0.218	P=0.8273, NS

12	Q Amplitude (mV)	Z=1.091	P=0.2752, NS
13	R Amplitude (mV)	Z=0.218	P=0.8273, NS
14	S Amplitude (mV)	Z=1.528	P=0.1266, NS
15	ST Height (mV)	Z=0.655	P=0.5127, NS
16	T Amplitude (mV)	Z=0.655	P=0.5127, NS

DISCUSSION & CONCLUSION

Terminalia Chebula significantly increases Time of appearance of tremors (P= 0.024); Time of appearance of RSR (P<0.05); Highly significant in increasing the time of appearance of Paralysis P<0.01); the time of appearance of IRDR (P<0.05); the time of appearance of convulsions (P<0.05); the time of appearance of LORR (P<0.05); the duration of survival period (P<0.05) as compared to control group when administered as antidote against Seed of *Thevetia Neriifolia*.

FDP against Seed of *Thevetia Neriifolia* causes highly significant increase in the time of appearance of tremors (P= 0.002)*;* appearance of paralysis (P< 0.05); appearance of LORR (P<0.05). It didn't caused any significant increase in time duration of appearance of RSR (P> 0.05); appearance of IRDR (P>0.05); appearance of Convulsions (P>0.05); duration of survival period (P>0.05) as compared to control group when administered as antidote against Seed of *Thevetia Neriifolia*..

FDP doesn't prove beneficial for the duration of appearance of RSR; duration of appearance of IRDR & duration of survival period but proved beneficial for appearance of tremors; appearance of Paralysis; appearance of convulsions and appearance of LORR as compared to control group.

But after comparing the results of *Terminalia Chebula* against Seed of *Thevetia Neriifolia* in experimental group for all the above mentioned criteria with that of standard group, no statistically significant variation of results observed. Hence *Terminalia chebula* proves to be beneficial than FDP as better antidote against SK.

Terminalia Chebula significantly increases time of appearance of tremors (P= 0.0143); time of appearance of RSR (P= 0.0196); time duration of appearance of Paralysis (P= 0.0429); significantly increases the time duration of appearance of IRDR RK (P= 0.0196); time of appearance of convulsions (P=0.0196); duration of survival period (P= 0.0455); But not found significantly effective to increase the time of appearance of LORR (P= 0.0619) when administered as antidote against root of *Thevetia Neriifolia* .

No significant changes occurred in heart rate, RR, T amplitude in any group, so no efficacy assessment can be done.

Terminalia chebula caused No changes for P duration; QRS interval; P amplitude; Q wave amplitude; R amplitude; ST height; T amplitude.

Terminalia chebula found statistically significant in preventing changes in PR interval; QTc against root of *T. neriifolia;* QT interval; T peak Tend interval; *S amplitude* against seed & root of *T. neriifolia;* JT interval against seed of *T. neriifolia.*

Maximum mean percentage decrease was observed in Experimental group *Terminalia chebula* against seed of *T. Neriifolia* whereas it was minimal in *Terminalia chebula* against root of *T. neriifolia.* FDP caused minimum decrease in BP against seed of *T. neriifolia.*

So, This study proposes *Terminalia chebula* for further clinical evaluation of its Antidote properties against *Thevetia neriifolia*

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Abbreviations	
Fructose 1,6 Diphosphate	FDP
Rapid and Shallow Respiration	RSR
Increased Rate and depth of Respiration	IRDR
Loss of Righting reflex	LORR
Beats Per Minute	BPM