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ACUTE AND REPEATED ORAL TOXICITY OF SIDDHA METALLO-MINERAL FORMULATION *SEENA RASA CHENDURAM* (SRC)

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ABSTRACT

Seena rasa chenduram (SRC) a Siddha drug which is prepared from Mercury, Sulphur and Alum is indicated for hemorrhoids and venereal diseases in the text Anuboga vaidhiya navaneetham. In siddha system of medicine metals and minerals are widely used to cure the diseases for many years. There is a need today to evaluate the safety profile of siddha mineral preparations. Acute and 28days repeated oral toxicity studies were performed according to OECD guidelines in Wistar Albino rats. In acute toxicity study the dose level of 5, 50,300, 2000mg/kg body weight was administered stepwise. 28 days repeated oral toxicity study was carried out at different dose levels X(9.36),5X(46.8),10X(93.6) and the control group of animals were administered vehicle only. Acute toxicity study concludes that LD50 of SRC is 1000mg and it comes under CAT- V (GHC) as per the OECD-423 classification. At the end of 28 days repeated oral toxicity study there were no abnormal signs were found during the study period. Acute and repeated oral toxicity studies of SRC revealed that SRC is safe for human consumption.

KEYWORDS: *Seena rasa chenduram*, Hemorrhoids, Toxicity study, Siddha drug, Mercury.

INTRODUCTION

The aim of the Siddha science is the reconstruction of the physical body and reconstruction of the spirit by which the body is being built. Siddha science is vast, it emphasized on the wellbeing of physical and mental aspect of the body. For medicine preparations they used the raw materials obtained from mineral, animal or vegetable origin. Siddha system is mainly based on the three humours are known as Vali, Azhal, Iyam. The imbalance between these three humours causes disease. This humoural pathology plays a vital role in Siddha medicine.

Diet also plays an important role in maintaining the three humours in the body. Therefore in the course of Siddha treatment patient should maintain the proper diet advised by the physician to prevent diseases.

The knowledge of poisons is one of the important branches of Siddha science. Siddhars have unparalleled knowledge in the description of dosage, toxicity and management of poisons.

Siddha system also deals with medicines prepared with metals. In Siddha system of medicine, metals and minerals are widely used to cure the diseases for many years. Siddhars were briefly explained the intoxication process of metals. Thus these metals are purified before the preparation to exclude their toxic effects. It is still more regrettable to note that no research work was taken up in this direction even during the time of Asiatic researches or even subsequently.

Thus *Seena rasa chenduram* which is prepared from Mercury *(Rasam),* Sulphur *(Gandhagam)* and Alum *(Padikaram)* is taken for the evaluation of its toxicity profile. The above ingredients are used to cure chronic, infectious, non infectious ailments in Siddha system of Medicine. As per the text, "*Seena rasa chenduram"* containing *Rasam* (Mercury), *Gandhagam* (Sulphur) and *Padikaram* (Alum) is indicated for moola noi (hemorrhoids) and mega noi(venereal diseases).This preparation was referenced from *Anuboga vaithiya navaneetham* part-3.

Until now there is no scientific evaluation is carried out for its toxicity profile. So there is a need of an hour to evaluate the safety studies on "*Seena rasa chenduram".* In this way, I prefer *"Seena rasa chenduram"* as my dissertation drug and to evaluate the toxicity profile. So, in the present investigation, it is aimed to perform acute and repeated oral toxicity studies. These studies are going to be conducted as per OECD guidelines.

MATERIALS AND METHODS

Seena rasa chenduram contains the following ingredients:

Purified *Padikaram*(alum)	–	1 *palam*(35gm).
Purified *Gandhagam*(sulphur)	_	3 *palam*(105gm).
Purified *Rasam*(mercury)	_	2 *palam*(70gm).

Collection

The raw drugs are obtained from the standard raw drug markets in Chennai, Tamilnadu.

Authentication

Drugs were identified and authenticated from department of Pharmacognosy in Siddha Central Research Institute, Chennai.

Method of Preparation of *seena rasa chenduram*

Purified *Rasam,* Purified *Gandhagam* and Purified *Padikaram* are packed in a container, buried in the husk and baked in *pudam*. Then the baked drug is powdered and taken.

METHODOLOGY

Selection of animal species

The preferred rodent species is the rat, although other rodent species may be used. Nulliparous and non-pregnant females with the strain of Wistar Albino rats were selected. Each animal, at the commencement of its dosing, was 6 to 8 weeks old and its weight lies in between 150-200g.

Housing and feeding conditions

The temperature in the experimental animal room was 22ºC (±3ºC). Although the relative humidity was at least 30% and preferably not exceeds 70% other than during room cleaning the aim was 50-60%. Lighting was artificial, the sequence being 12 hours light, 12 hours dark. For feeding the pellet diet with an unlimited supply of RO water was used. Animals were group-caged by dose, but the number of animals per cage did not interfere with clear observations of each animal.

Administration of doses

Seena rasa chenduram suspended in 10% Aqueous Tween 80 with vigorous mixing and was administered to the groups of Wistar rats in a single oral dose with different dose levels by garage using a feeding needle. The control group received an equal volume of the vehicle.

Animals were fasted prior to dosing. Following the period of fasting, the animals were weighed and then the test substance was administered. Three animals are used for each step. The dose level of 5, 50, 300 and 2000 mg/kg body weight was administered stepwise. After the substance has been administered, food was withheld for a further 3-4 hours. The principle of laboratory animal care was followed. Observations were made and recorded systematically and continuously observed as per the guideline after substance administration. The visual observations included skin changes, mobility, and aggressiveness, sensitivity to sound and

pain, as well as respiratory movements. They were deprived of food, but not water 16–18 h prior to the administration of the test suspension. Finally, the number of survivors was noted after 24 h and these animals were then maintained for a further 14 days and observations made daily. The toxicological effect was assessed on the basis of mortality

Test substance and Vehicle

The *Seena rasa chenduram* is freely soluble in water and the suspension was made with tween80 solution for dose accuracy and easy administration in animals.

The justification for choice of vehicle

The vehicle selected as per the standard guideline which is pharmacologically inert and easy to employ for new drug development and evaluation technique.

Test animals and Test conditions

Sexually mature female sex Wistar albino rats (150-200g) were obtained from Srinivasa animal laboratory, Bangalore. All the animals were kept at an animal house in National Institute of Siddha, Chennai under standard environmental condition (22±3°C). The animals had free access to water and standard pellet diet (Sai meera foods, Bangalore). Rats were deprived of food but not water 12h prior to administration of the *Seena rasa chenduram*. The principles of laboratory animal care were followed and the Department‘s ethical committee approved the use of the animals and the study design.

The toxicity studies were evaluated after getting permission from the Institutional Animal Ethical Committee certificate. IAEC PROTOCOL NO: 1248/ac/09/CPSEA/4-39/2O11.

Acute oral toxicity study (OECD guidelines – 423)

Species and strain	: Wistar Albino rat
Sex	: Female
Age/Weight	: 6 weeks/150-200 gm
Test guideline	: OECD guidelines - 423
Groups/treatment	: Grouped by randomization Duration of exposure to the
“ Seena rasa chenduram”	*:* Single dose
Study duration	: 14 days
Number of animals	: 3 females/group
Route of administration	: Oral

Groups	No of Rat
Group I Vehicle control (Ghee)	3 female
Group II Test drug – 5mg/kg b. wt	3 female
Group III Test drug – 50 mg/kg b. wt	3 female
Group IV Test drug – 300 mg/kg b. wt	3 female
Group V Test drug – 2000 mg/kg b. wt	3 female

Acute oral toxicity of the formulations were evaluated in rats following OECD guideline - 423. Animals were divided into five groups, each group containing 3 females weighing 150 - 200g with age of 6 weeks. One group as control and the other four groups were treated with test drug at four different doses (5mg, 50mg, 300mg, 2000mg/kg.b.wt) by oral gavages.

Behavior

The animals were observed closely for behavior in the first four hours which includes abnormal gait, aggressiveness, exophthalmos, ptosis, akinesia, catalepsy, convulsion, excitation, head twitches, lacrimation, loss of corneal reflex, loss of traction, piloerection reactivity of touch, salivation, scratching, sedation, stereotypes (chewing), stereotypes(head movements), stereotypes (sniffing), tremor and writhes, diarrhea, leathery, sleep and coma.

Body weight

Body weights were recorded on day 1, 2, 7 and 14 of the study.

Mortality

Animals were observed for mortality throughout the entire period.

Gross necropsy

At the end of 14th day animals were sacrificed for gross necropsy. It includes examination of the external surface of the body, all orifices, and organs like brain, lungs, heart, spleen, liver, stomach, kidneys, sadrenals and sex organs of all animals.

RESULTS

Results are summarized as the number of animals displaying signs of toxicity, the number of animals found dead during the test or killed for humane reasons, time of the death of individual animals, a description and the time course of toxic effects and reversibility, and necropsy findings.

28 Days Repeated Oral Toxicity Study of Seenarasa Chenduram Oecd - 407

Species and strain	:	Wistar albino rats
Sex	:	Male and Female
Age/Weight	:	6 weeks/150-200mg
Test guideline	:	OECD guidelines – 407
Groups/treatment	:	Grouped by randomization
Duration	:	28 days
Number of animals	:	6/group (3/sex)
Route of administration	:	Oral

Groups	No of R ats
Group I Vehicle control (Ghee)	6 (3male,3 female)
Group II test drug - low dose (X)	6 (3male,3 female)
Group III test drug - Mid dose (5X)	6 (3male,3 female)
Group IV test drug - High dose (10X)	6 (3male,3 female)

The study will be carried out as per OECD Guideline 407 (Repeated Dose 28-Day Oral T oxicity in Rodents). The animals will be divided into four groups each group consist of 6 animals (3 males and 3 females). One group will serve as control and the other three groups for test drug at three different dose levels (low, mid and high) for 28 days.

ANIMAL SOURCE

Test animals were obtained from The King Institute, Chennai and kept at animal house, National Institute of Siddha, Chennai. All the animals were kept under standard environmental condition (22 ± 3ºc), The animals had free access to water and standard pellet diet (Sai Meera foods Pvt. Ltd, Bangalore). The principles of laboratory animal care were followed.

IDENTIF ICATION OF ANIMAL

Animals were identified by cage number and individual marking on the fur of each animal with picric acid. Each animal was marked with picric acid. The females were nulliparous and non pregnant.

Housing and Environment

The animals were allowed for an acclimatization period of 7 days to laboratory conditions prior to the initiation of treatment. The animals were housed in polypropylene cages provided with bedding of husk. Dark and light cycle each of 12 hours was maintained.

ADMINISTRATION PERIOD

28 days Dose Se Lection

A repeated oral toxicity study was carried out at different dose levels (x, 5x, 10x).

Preparation And Administration of Dose

Seena rasa chenduram was suspended in 10% aqueous tween 80 solution. It was administered to groups I, II, IIIat dose levels of(x(9.36), 5x(46.8), 10x(93.6)). The control animals were administered vehicle only. The administration was given orally by using an oral gavage once in daily for 28 days.

Observations body weight

During the study, the body weight of the animals was evaluated weekly once.

Food and water intake

Water and food consumption were calculated daily.

Mortality

Animals were observed for mortality daily.

LABORATORY INVESTIGATIONS

Collection of Blood

Blood was collected in all overnight (12 hours) fasted rats through cardiac puncture method and it will be processed for below mentioned investigations.

Laboratory test

Complete Haemogram, Renal function test, Liver function test.

Necropsy

By the end of 28 days, the animals were sacrificed by excessive anesthesia. Animals were subjected to gross necropsy. Vital organs collected from the animals were subjected to histopathology.

Histopathology

Animals were subjected to histopathological investigations. Organs like heart, lungs, kidney, liver, spleen, stomach were collected from all animals and preserved in 10% buffered neutral formalin, sliced 5 or 6µm sections and it will be stained with hematoxylin and eosin, examined for histopathological changes.

Statistical Analysis

Findings such as clinical sings of intoxication, body weight changes, food consumption, hematology, and biochemical parameters were subjected to one-way ANOVA followed by Dunnet "t" test using a computer software programme-INSTAT -V3 version.

RESULTS AND DISCUSSION

Results of Acute Oral Toxicity Study

All the data were summarized in the form of a table. Table (1) Showing the animals behavioral signs in control and test groups.

At the dose level of 5 and 50 mg/kg body wt there were no abnormal signs were detected. No abnormality in necropsy findings.

At the dose level of 300mg/kg body wt animals show the following toxic signs on the 2nd after drug administration.

EYES: Protruded HINDLIMB: Extended GRIP: Power decreased FOOD INTAKE: Normal WATER INTAKE: Normal

On 7th day nasal discharge is seen. Eyes were normal.

On 12th day animals show normal behavioral signs. And toxic signs were reversible. On 14th day there was no abnormality in necropsy findings.

At the dose level of 2000mg/kg body wt animals show the following toxic signs:
EYES: Protruded HINDL IMB: Extended GRIP: Power decreased

FOOD INTAKE: Normal WATER INTAKE: Normal BODY WEIGHT: Normal

On examination generalized bulging seen. Nasal bleeding is seen. Muscular Inco-ordination was seen. Muscular spasm was seen.

Two animals found dead on the 5th day.

Necropsy findings of 2000mg/kg body weight dead animals: Lung congestion seen Ulceration in stomach was seen.

Remaining one animal in 2000mg group shows no abnormal findings in Necropsy.

This concludes that LD50 of Test drug is 1000mg and it comes under CAT-V (GHC) as per the OECD-423 classification.

RESULTS OF 28 DAYS REPEATED ORAL TOXICITY STUDY

Clinical signs

No abnormal behavioral signs were observed during the study period.

Mortality

The test drug *Seena rasa chenduram* did not cause any mortality in X, 5X and 10X dose levels and were considered as safe dose levels.

Body Weight

Both control and test dose groups exhibited body weight gain throughout the administration period of 14 days. Table (2).

Food consumption

No difference in food intake of control and test group animals observed during the period of study. Table (3).

Water Intake

No difference in water intake of control and test group animals observed during the period of study. Table (4)

Hematological investigation

The results of hematological investigation conducted at the end of the study, test groups revealed no significant changes in values of different parameters, when compared with the control group. The Hb count was slightly elevated in test groups, but statistically not significant when compared with the control group. Table (5).

Biochemical investigations

Biochemical investigations were conducted at the end of the study and the results were recorded. In test groups there was no significant elevation in the levels of biochemical parameters, when compared with the control group. And the values obtained were within normal biological limits. Table (6, 7, 8).

Histopathology

Gross pathological examination of animals doesn't' t reveal any abnormalities in control groups. The histopathological study of the organs such as heart, lungs and kidney were normal in control, X, and 5X and 10X groups. In 10X groups the stomach shows ulceration in Stomach, Liver shows Lymphocyte infiltration.

Acute Toxicity Study of *Seena Rasa Chenduram*

Table 1: Dose finding experiment and its behavioral Signs of Toxicity.

No	Dose mg/kg	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	10
1.	5	+	-	-	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
2	50	+	-	-	-	+	+	-	-	-	-	-	-	-	-	-	-	-	-	-	-
3	300	+	-	-	+	+	+	-	+	-	-	-	-	-	-	-	-	-	-	-	-
4	2000	+	-	-	+	+	+	-	+	-	-	-	-	-	-	-	-	+	-	-	-

1.Alertness 2.Aggressiveness 3.Pile erection 4.Grooming 5.Gripping 6.Touch Response 7. Decreased Motor Activity 8.Tremors 9.Convulsions 10.Muscle Spasm 11.Catatonia 12.Muscle relaxant 13.Hypnosis 14.Analgesia 15.Lacrimation 16.Exophthalmos 17.Diarrhoea 18.Writhing 19.Respiration 20.Mortality

Table – 2: 28 Days Repeated Oral Toxicity Study of *Seena Rasa Chenduram* Body Weight of Wistar Albino Rats Group Exposed To *Seena Rasa Chenduram*

Dose	Body weight (gms/rat)				
	Da y 1	Da y 7	Da y 14	Da y 21	Da y 28
CONTROL	159±5.51	162.67±2.42	165.33±2.42	166.17±1.94	167.83±2.32
X	162.83±6.77	165±6.54	166.33±6.56	168±6.36	171.67±5.79
5X	171.67±6.62	173.83±3.67	175.50±6.06	176.67±5.92	178.17±5.91
10X	172.50±1.87	173.83±1.60	175.17±1.17	176.50±1.05	177.50±1.05
P VALUE	>0.05 N.S	>0.05 N.S	>0.05 N.S	>0.05 N.S	>0.05 N.S

Values are mean of 6 animals ±S.D, N.S-Non significance

Table 3: Food Intake of Wister Albino Rats Group Exposed To *Seena Rasa Chenduram.*

Dose	Food intake (gms/rat)			
	Day 1	Day 7	Day 14	Day 28
Control	31.16±3.31	38.83±5.91	40.16±4.07	41.47±5.42
X	32.74±3.27	34.31±4.17	38.25±3.68	39.76±3.41
5X	40.16±4.08	39.16±2.73	41.15±5.10	41.40±5.31
10X	35.25±3.5	35±2.60	40.16±3.54	40.51±4.73
P V A L UE	>0.05 N.S	>0.05 N.S	>0.05 N.S	>0.05 N.S

Values are mean of 6 animals ±S.D, N.S-Non significance

Table 4: Water Intake of Wister Albino Rats Group Exposed *Seena Rasa Chenduram.*

Dose	Water In Take (Ml/Rat)			
	Day 1	Day 7	Day 14	Day 28
Control	48.41±6.52	50.32±5.21	48±4.11	49±5.18
X	50.66±3.55	47.5±2.73	41.66±2.58	40.12±2.36
5x	48.336.05	49.33±3.67	43±3.48	40±3.21
10x	49.16±4.91	58.33±5.16	46.83±5.11	43.35±5.14
P value	>0.05 N.S	>0.05 N.S	>0.05 N.S	>0.05 N.S

Values are mean of 6 animals ±S.D, N.S-Non significance

Table 5: Effect of *Seena Rasa Chenduram* on Hematological Parameters.

Investigation	Control	Group 1	Group 2	Group 3	P value
Hb %	12.23 ±0.10	13.25±0.24	12.25±0.14	12.53±0.18	>0.05 N.S
T c cells/ mm3	9050±104.88	8966.67±121. 11	8850±187.08	8216.67±147.20	>0.05 N.S
Polymorphs %	36.5±26.2	58±2.5	46.8±17.5	38.6±20.5	>0.05 N.S
Lymphocytes%	58±19.8	41.5±2	52.5±16.9	59.3±9.03	>0.05 N.S
Esinophils%	1.67±1.03	2.33±1.63	2.17±1.47	1.50±0.55	>0.05 N.S
Platelet	4.45±.75	3.26±0.39	3.23±0.22	3.26±0.23	>0.05 N.S
Monocyte	0.50±.55	0.33±.52	0.50±0.55	0.50±0.55	>0.05 N.S

Values are mean of 6 animals ± S.D, N.S- Non significance

Table 6: Bio Chemical Parameters Effect of *Seena Rasa Chenduram* on Blood Sugar And Lipid Profile.

Investigation Mg/dl	Contro l	Group 1	Group 2	Group 3	P value
B.glucose	98.3±38.3	74.8±4.7	78.3±8.3	81.2±9.3	>0.05 N.s
T.cholestrol	65.5±3.5	66.33±3.4	70.3±4.0	76±5.2	>0.05 N.s
Tgl	135±13.1	103.3±14.1	111.4±20.5	121±5.2	>0.05 N.s
Hdl	20±3.9	22.12±2.1	23.1±3.16	25.8±3.8	>0.05 N.s
Ldl	17.9±2.0	22.43±4.1	24.4±4.2	25.3±3.3	>0.05 N.s
Vldl	25±2.2	21.7±3.04	22.1±4.2	23.8±1.7	>0.05 N.s

Values are mean of 6 animals ± S.D, N.S- Non significance

Table-7: Effect of *Seena Rasa Chenduram* on Renal Parameters.

Investigation	Control	Group 1	Group 2	Group 3	P value
Urea mg/dl	27.7±14.8	33.7±4.0	23 ±7.2	25.8± 2.4	>0.05 N.S
Creatinine mg/dl	0.64±.10	0.74± 0.07	0.60± 0.07	0.68± 0.08	>0.05 N.S
Uric acid mg/dl	2.40±.08	2.26±.33	2.28±.61	2.2±.49	>0.05 N.S
Calcium m.eq/l	8.4± 0.7	8.6± 0.62	8.3± 1.06	9.2± 0.43	>0.05 N.S
Phosphorous m.eq/l	2.78±.06	3.0 ±.58	2.6±0.89	3.4±0.50	>0.05 N.S

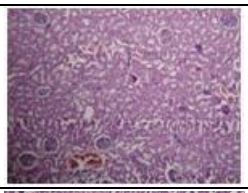
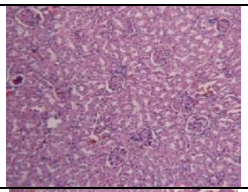
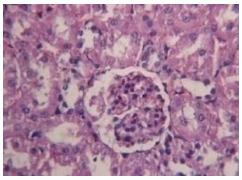
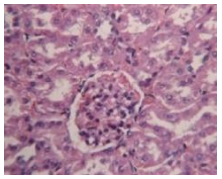
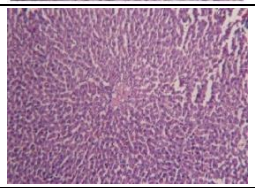
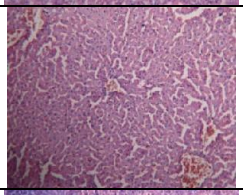
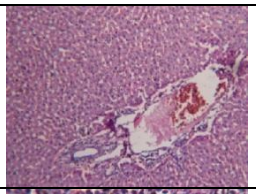
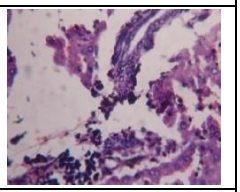
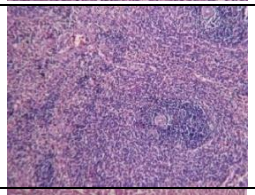
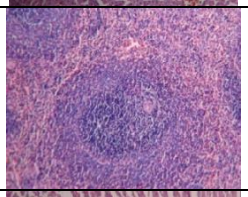
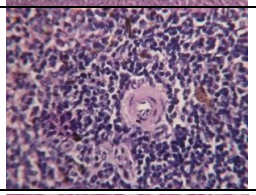
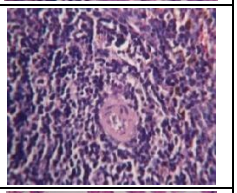
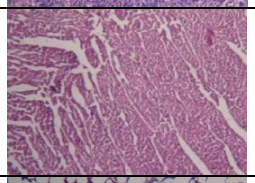
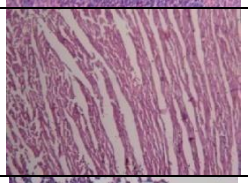
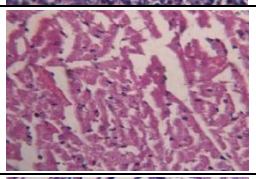
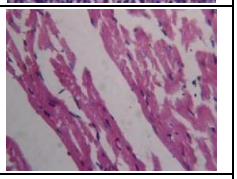
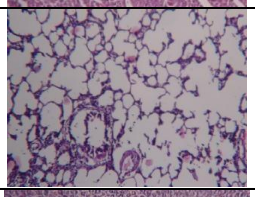
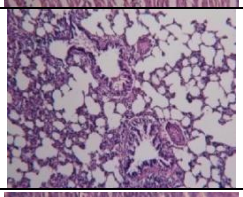
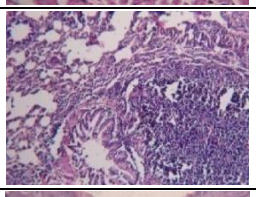
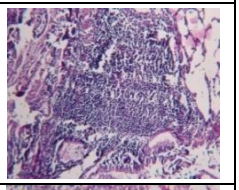
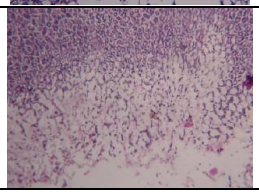
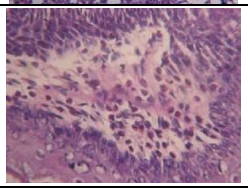
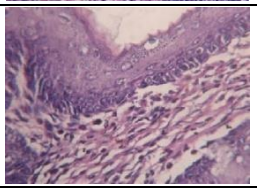
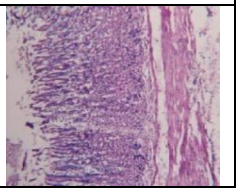
Values are mean of 6 animals ± S.D, N.S- Non significance

Table-8: Effect of *Seena Rasa Chenduram* on Hepatic Parameters.

Investigation	Control	Group 1	Group 2	Group 3	P value
T. Bilirubin mg/dl	0.7±.09	0.7±0.12	0.71±0.15	0.60±0.08	>0.05 N.S
Dir. Bilirubin mg/dl	0.2±0.07	0.3±0.05	0.34±0.08	0.24±0.04	>0.05 N.S
Ind. Bilirubin mg/dl	0.4±0.06	0.35±0.11	0.35±0.10	0.34±0.07	>0.05 N.S
SGOT U/L	53±6.9	71.7±23.46	50.1±5.0	62.1±18.80	>0.05 N.S
SGPT U/L	60±8.2	80.5±32.6	65.3±11.5	73.8±19.3	>0.05 N.S
A lk.ph U/L	140±7.6	141.6±15.0	147.3±18.1	143.3±8.03	>0.05 N.S
T otal protein g/dl	6.5±0.39	7.09±0.36	6.75±0.61	6.66±0.29	>0.05 N.S
A lbumin g/dl	3.03±0.33	3.38±0.23	3.4±0.33	3.48±0.31	>0.05 N.S
Globulin g/dl	3.46±0.07	3.54±0.43	3.38±0.39	3.0±0.22	>0.05 N.S

Values are mean of 6 animals ± S.D, N.S- Non significance

Histopathology report of *Seena rasa chenduram*

Organs	Control	Low dose	Mid dose	High dose
Kidney				
Liver				
Spleen				
Heart				
Lungs				
Stomach				

DISCUSSION

In Acute toxicity study period there were reversible toxicity signs in 300mg group. In the 5 and 50mg group animals there were no abnormal toxicity signs. Two animals were found dead in 2000mg/ kg body weight dose. There were no reduction in body weight of animals were observed in the study period. It concludes that L D 50 of *Seena rasa chenduram* is 1000mg/ kg body weight CAT-V(GHC) as per the guideline OECD- 423.

Repeated oral toxicity study was conducted for about 28 days as per the OECD guideline-407 in 3 doses X (9.36), 5X (46.8), 10X (93.6).Animals were observed throughout the period.

After 28 days animals were sacrificed and blood samples were collected, investigated and the results revealed that there were obvious changes in Hb and mild changes in other hematological parameters compared to control group. Finally all the reports were statistically calculated. There was no significant change in body weight, water and food intake, hematological and bio chemical parameters.

The histopathological study on the organs such as heart, lungs, kidney, spleen and liver was normal in control, low dose, and mid dose groups. In high dose group in liver portal tract shows lymphocyte infilteration. The lung shows focal lymphoid aggregations in high doses.

CONCLUSION

As the result of this study,it has been concluded that, The Acute and Repeated oral toxicity study of *Seena rasa chenduram* is found to be Less toxic and the therapeutic dose level mentioned in the literature is safe for human Consumption.

ACKNOWLEDGEMENT

I express my heartfelt gratitude to my Institute NATIONAL INSTITUTE OF SIDDHA, CHENNAI It would not be fair if I donot regret for all the animals that lost their lives for the sake of my study and without which I wouldnot have been successful in my study.

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