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ACUTE ORAL TOXICITY STUDY OF SIDDHA DRUG NARKARANTHAI LEGIUM IN FEMALE WISTAR RATS

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ABSTRACT

In Siddha system of traditional medicine, Narkaranthai Legium (NKL) is an Herbal formulation. In the reference text of Brahma muni karukidai soothiram 380. It has been used for the treatment of psoriasis. Psoriasis is a long lasting autoimmune disease characterized by patches of abnormal skin. These skin patches are typically red, dry, itchy, and scaly. On people with darker skin the patches may be purple in colour. Psoriasis varies in severity from small, localized patches to complete body coverage. Siddha medicine NKL is a good remedy for the treatment of psoriasis. In this study the author has aimed to evaluate safety and efficacy of the trail drug NKL in female Wistar rats (Nulliparous, Non-Pregnant). Acute oral toxicity was performed as per organization for economic co-operation for the development (OECD) guideline 423 methods. Acute toxicity studies were carried out in 5 groups of 15 female Wistar rats, a dose of 500mg, 1000mg, 2000mg, 4000mg and 6000mg of NKL was administered and monitored for any toxicity effects. The trail medicine Narkaranthai legium was Non-toxic in acute toxicity study.

KEYWORDS: Siddha medicine, Narkaranthai Legium, Acute toxicity study, Female Wistar rats, Pre-clinical study.

INTRODUCTION

Psoriasis is a common, chronic, and recurrent inflammatory diseases of the skin characterized by circumscribed, erythematous, dry, scaling plaques of various sizes. The lesions are usually

covered by silvery white lamellar scales.[1] Siddha literatures have prescribed so many medicines for the treatment of psoriasis. In Siddha system, Narkaranthai legium[2] is a poly herbo mineral medicine, prescribed in Siddha text book Brahma muni karukadai soothiram 380 for psoriasis. The pre-clinical toxicity screening is essential for determining a safe dose for the human trails.[3] Consequently an effort has been made by the author to evaluate acute toxicity of the siddha poly herbo mineral preparation NKL in laboratory animals.

MATERIALS AND METHODS

The drugs were purchased from the local market in Thirunelveli Town, and authenticated by Department of pharmacology, Government Siddha Medical College, Palayamkottai, Tamilnadu, India. The drugs were purified and the medicine was prepared as per the methodology in the Siddha text Brahma muni karukadai soothiram 380. The drugs used to prepare Narkaranthai Legium are.

S. No.	Botanical name	Tamil name	Family
1	*Sphaeranthus indicus*	*Kottai karanthai*	*Astraceae*
2	*Nigella sativa*	*Karunjeeragam*	*Ranunculaceae*
3	*Terminalia chebula*	*Kadukkai*	*Combretaceae*
4	*Terminalia bellirica*	*Thandrikai*	*Combretaceae*
5	*Acorus calamus*	*Vasambu*	*Acoraceae*
6	*Piper longum*	*Thippili*	*Piperaceae*
7	*Piper nigrum*	*Milagu*	*Piperaceae*
8	*Sassuria lappa*	*Koshtam*	*Asteraceae*
9	*Zingiber officinale*	*Chukku*	*Zingiberaceae*
10	*Clerodendrum serratum*	*Siruthekku*	*Verbenaceae*
11	*Psoralea corylifolia*	*Karbokarisi*	*Fabaceae*
12	*Plumbago zeylanica*	*Chithramoolam*	*Plumbaginaceae*
13	*Celastrus paniculatus*	*Valuzhuvai arisi*	*Celastraceae*
S.no	**Minerals**	**Tamil name**	**English name**
14	*Sodium chloride impura*	*Indhuppu*	*Rock salt*
15	*Hydragyrum sub chloride*	*Rasa karpooram/ pooram*	*Calomel*
S.no	**English name**	**Tamil name**	
16	*Palm jaggery*	*Panai vellam*	
17	*Sugar cane*	*Sarkarai*	
18	*Ghee*	*Nei*	
19	*Honey*	*Thaen*	

Purification of raw drugs

- ✓ Sphaeranthus indicus- Dried in shade *(Sarugu patham)* powder form.
- ✓ Nigella sativa- It is fried in Golden Colour.
- ✓ Terminalia chebula- It is fried in Golden Colour and removes internal seed.

- ✓ Terminalia bellirica- It is fried in Golden Colour.
- ✓ Acorus calamus- It is burned and dried in shade.
- ✓ Piper longum- It is dried and mildly fried with heat.
- ✓ Piper nigrum- It is dried and mildly fried with heat.
- ✓ Indhuppu- Dissolved in kaadi (vinegar) and filtered then dried in sunlight[4].
- ✓ Valuzhuvai arisi- It is mildly fried and dried it.
- ✓ Koshtam- It is mildly fried and dried in shade.
- ✓ Chukku- removed the outer skin of dried ginger and coated with slaked lime and allows it for 3 hrs.[4]
- ✓ Siruthekku- It is mildly fried and dried in shade.
- ✓ Karbokarisi- It is mildly fried and dried in shade.
- ✓ Chithramoolam- Bark of root is extract and backed with steam of milk.
- ✓ Rasa karpooram (calomel) - Take Piper betel *(kammaaru vetrilai)* and Piper nigram (Milagu) for 8.75 gms, then grained with water and formed kalkam and then mixed with water in 1.3 litre, then take 35gram calomel and covered with cloth and then dissolved in Thula yanthiram. Then heat with flame for mild heat *(Dheebakkini)* till the water in decreased in ¾ its level. Then take calomel and washed with water and dried in sunlight.[5]

Preparation and storage

All these ingredients from 1 to 15 are purified and powdered it into fine and coarse powdered, and then palm jaggery purified and powdered into fine, and then above coarse powdered and mixed with palm jaggery and sugar mixed well. Then heating with vessel. Then add cow's ghee and then finally add honey. This is then heating into legiya patham decanted in another vessel and allowed to cool the legiyam and preserved in clean dry air tight container. Narkaranthai Legium is brownish in colour and sticky in nature.

Acute Oral Toxicity

Acute toxicity study of Narkaranthai Legium (NKL) was done adhering to the guidelines of OECD 423 method.[6] The study was done in KMCH College of pharmacy, Coimbatore, after obtaining the needed approval for the study from the Institutional Animal Ethical Committee (IAEC) ***Ref.no: KMCRET/MD(S)/01/2016-17.*** Fifteen healthy young adult female Wistar rats, nulliparous and non-pregnant weighing about 150-200gm were selected for the study. The rats were divided into 5 groups, with 3 animals in each group. 1500mg/kg dosage of the

test drug in 200g body weight was given in a single dose of 1ml. Distilled water was used as the vehicle for per oral administration of the drug through oral gavage.

Housing and feeding conditions

Room temperature	22°C ± 3°C
Humidity	40-60%
Light	12 h : 12h (light : dark cycle)
Feed	Standard laboratory animal food pellets with water ad libitum

Study period and observation parameters

Initial once observation	First 30 minutes and periodically 24 h
Special attention	First 1-4 hr after drug administration
Long term observation	Up to 14 days
Direct observation parameters	Tremors, convulsions, salivation, diarrhoea, lethargy, sleep and coma.
Additional observation parameters	Skin and fur, eyes and mucous membrane, respiratory, circulatory, autonomic and central nervous systems, somato motor activity and behaviour pattern etc.

Study procedure

Acute oral toxicity was performed as per organization for economic co-operation for development (OECD) guideline 423 methods. NKL was administered in a single dose by tuberculin syringe. Animals are fasted 3 hr prior to dosing (food was withheld for 3 hr but not water). Following the period of fasting animals was weighed and test substance was administered orally at a dose of 500mg, 1000mg, 2000mg, 4000mg and 6000mg/kg. After NKL administration, food was withheld 2 hr in mice. Animals are observed individually after at least once during the first 30 min, periodically during the first 24 hrs, with special attention given during the first 4 hrs, and daily thereafter, for a total of 14 days.

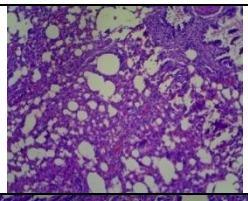
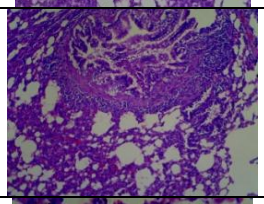
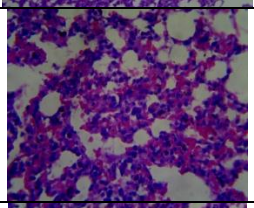
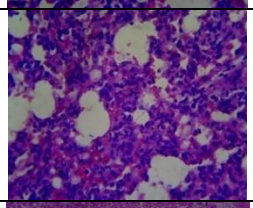
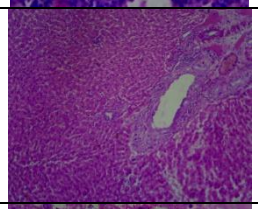
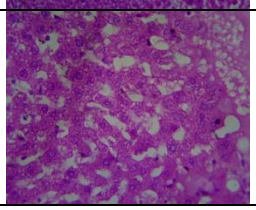
OBSERVATIONS

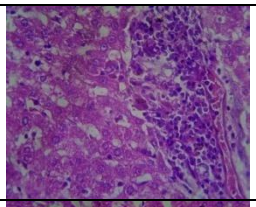
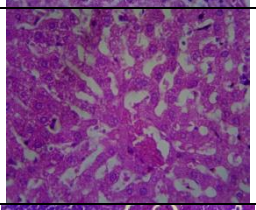
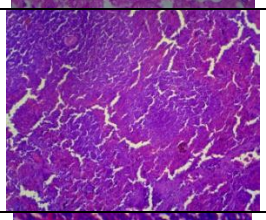
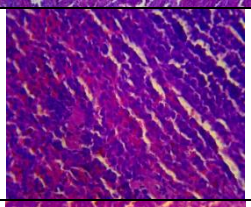
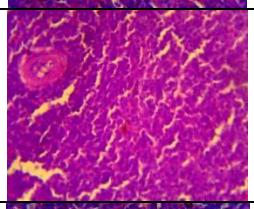
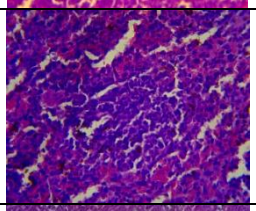
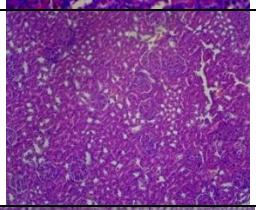
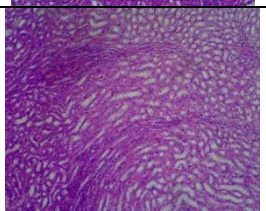
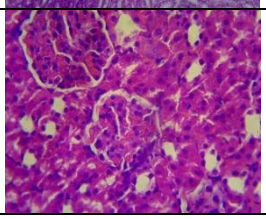
Effect of Narkaranthai Legium on acute toxicity test in mice

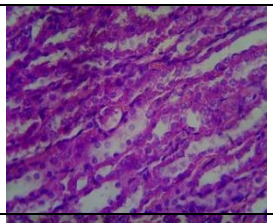
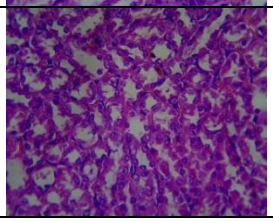
S. No.	Response	Head		Body		Tail	
		Before	After	Before	After	Before	After
1	Alertness	Normal	Normal	Normal	Normal	Normal	Normal
2	Grooming	Absent	Absent	Absent	Absent	Absent	Absent
3	Touch response	Absent	Absent	Absent	Absent	Absent	Absent
4	Torch response	Normal	Normal	Normal	Normal	Normal	Normal
5	Pain response	Normal	Normal	Normal	Normal	Normal	Normal
6	Tremors	Absent	Absent	Absent	Absent	Absent	Absent
7	Convulsion	Absent	Absent	Absent	Absent	Absent	Absent

8	Righting reflux	Normal	Normal	Normal	Normal	Normal	Normal
9	Gripping strength	Normal	Normal	Normal	Normal	Normal	Normal
10	Pinna reflux	Present	Present	Present	Present	Present	Present
11	Corneal reflux	Present	Present	Present	Present	Present	Present
12	Writhing	Absent	Absent	Absent	Absent	Absent	Absent
13	Pupils	Normal	Normal	Normal	Normal	Normal	Normal
14	Urination	Normal	Normal	Normal	Normal	Normal	Normal
15	Salivation	Normal	Normal	Normal	Normal	Normal	Normal
16	Skin colour	Normal	Normal	Normal	Normal	Normal	Normal
17	Lacrimation	Normal	Normal	Normal	Normal	Normal	Normal

Histopathological examination

S. No.	Specimen		Observations
1a	Lung Ref. no: [H0 464A/17]		10× shows dense interstitial mild inflammation (Not significant)
1b			10 × shows lung parenchyma with peribronchiole mild inflammation (Not significant)
1c			40 × shows mild inflammatory infiltrates (Not significant)
1d			40 ×shows interstitial infiltrates (Not significant)
2a	Liver Ref. no: [H0 464B/17]		10×shows altered lobular architecture
2b			40×shows cytoplasmic vacuolation

2c			40×periportal inflammation
2d			40×shows sinusoidal dilatation and central vein congestion
3a	Spleen Ref. no: [H0 464C/17]		10×shows normal spleen
3b			40×shows normal red and white pulp
3c			40×shows normal white pulp and pencillar artery
3d			40×shows normal white pulp
4a	Kidney Ref. no: [H0 464D/17]		10×shows kidney with glomeruli and tubules
4b			10×shows normal interstitium
4c			40×shows normal glomeruli

4d			40×shows normal interstitium
4e			40×shows normal tubules

RESULTS

From acute toxicity study it was observed that the administration of Narkaranthai Legium did not induce drug related toxicity and mortality in the animals up to 6000mg/kg in 200gm female Wistar rats. So No-Observed-Adverse-Effect- Level (NOAEL) of NKL is 6000 mg/kg equal to human dose.

DISCUSSION

Narkaranthai Legiyam was administered single time at the doses of 500mg, 1000mg, 2000mg, 4000mg and 6000mg/kg to female Wistar rats and observed for consecutive 14 days after administration. Doses were selected based on the pilot study and literature review. All animals were observed daily once for any abnormal clinical signs. Weekly body weight and food consumption were recorded. No mortality was observed during the entire period of the study. Data obtained in this study indicated no significance physical and behavioural signs of any toxicity due to administration of NKL at the doses of 500mg, 1000mg, 2000mg, 4000mg and 6000mg/kg to female Wistar rats.

At the 14th day, all animals were observed for functional and behavioural examination. In functional and behavioural examination, home cage activity, hand held activity were observed. Home cage activities like Body position, Respiration, Clonic involuntary movement, Tonic involuntary movement, Palpebral closure, Approach response, Touch response, Pinna reflex, Sound responses, Tail pinch response were observed. Handheld activities like Reactivity, Handling, Palpebral closure, Lacrimation, Salivation, Piloerection, Papillary reflex, abdominal tone, Limb tone were observed. Functional and behavioural examination was normal in all treated groups. Food consumption of all treated animals was found normal as compared to normal group.

SUMMARY

The present study was conducted to know single dose toxicity of Narkaranthai legiyam on female Wistar rats. The study was conducted using 15 female Wistar rats. The female animals were selected for study of 8- 12 weeks old with weight range of within ± 20% of mean body weight at the time of randomisation. The groups were numbered as group I, II, III, IV and V and dose with 500mg, 1000mg, 2000mg, 4000mg and 6000mg/kg of Narkaranthai legiyam. The drug was administered by oral route single time and observed for 14 days. Daily the animals were observed for clinical signs and mortality. There were no physical and behavioural changes observed in Female Wistar rats during 14 days. Mortality was not observed in any treatment groups.

CONCLUSION

The study shows that Narkaranthai legiyam did not produce any toxic effect at low dose of 500mg, 1000mg, 2000mg, 4000mg and 6000mg/kg to rats. So No-Observed-Adverse-Effect-Level (NOAEL) of Narkaranthai legiyam is 6000 mg/kg. NKL was Non-toxic in acute toxicity study.

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