A Chronic toxicity of *Urai mathirai*- Siddha Herbal Formulation in wistar albino rats

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ABSTRACT

The present study was to carry out 90 days repeated oral toxicity of Urai mathirai in wistar albino rats.The chronic toxicity study was carried out as per (OECD) test guideline 408 and Central Council for Research in Ayurvedic Sciences (CCRAS) respectively. In this study, theUrai mathirai drug solution was administered at dose of (10, 50 and 100mg/kg b.wt) for every 24 hours orally upto 90 days for all the three groups. At the end of each study, hematological and biochemical analysis were evaluated. Histopathological examination of vital organs of the rats were taken for gross findings, compared to controls. Distilled water aided as a control in all the tests. There was no significant difference ($p > 0.05$) observed in the relative organs weight, body weight, hematological, biochemical parameters, and gross abnormalities when compared to the control. No mortality was recorded with respect drug effect.The results may lead that the oral administration of the Urai mathiraiat doses of 10, 50 and100 mg/kg.b.wtdoes not showedany toxicity effect in wistar rats during the experimental period.

- ***Whatisalreadyknownaboutthissubject:***
  - InSiddhasystem,Uraimathiraihasbeenprescribedbydoctorstoimprovetheimmunityinchildren and there is lack of scientific evidence (Toxicity and safer dose levels).
  - Inordertoensurethescientificdatai.echronictoxicity(NOAEL)effecthasbeen evaluatedwiththe help of animal models
- ***Whatthisstudyadds:***
  - ThisChronictoxicitystudyrevealsaboutthemaximumdoselevelof100mg/kgbodyweightwas found to be safe and it doesn't produce any toxic effects related to our drug over the animal model.
  - HenceourstudyensuresUraimathiraiwasfoundtobesafeupto100mg/kgbodyweight.

Keywords: Chronic toxicity; Herbal formulation; Siddha and Urai mathirai.

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1. Introduction

Traditional systems of medicine play a vital role in meeting the global healthcare needs. There are various recognized medical systems in India. They are Ayurveda, Siddha, Unani, Yoga, Naturopathy Homeopathy and Sova Rigpa (Patwardhan, B;2005). Among them, Siddha is a unique system of medicine that originated in Tamil Nadu and has its roots in the Tamil language. The word "Siddha" literally means "established truth". Siddha medicine is said to reduce the root cause of diseases by maintaining the balance of Vata, Pitha and Kapha. The origin of the Siddha system of medicine is attributed to the ancient saints Siddhas (Elankani, P.,2019). The increase in the use of herbal products worldwide has been due not only to traditional knowledge but also to improved availability through formal and informal markets. A recent scoping review has highlighted the wide variation in consumption patterns across regions and highlighted the influence of regulatory policies, cultural practices and socioeconomic factors on the use of herbal products. (Thanat Nakaphan et al., 2025).

Urai Mathirai is a medicine that has been used for the past three decades in the form of long finger-sized bullets, which are rubbed and given to children through breast milk to improve immunity, often resulting in freedom from health hazards such as respiratory infections/gastrointestinal infections and anorexia. For global acceptance, this medical system will undergo scientific validation, i.e., upgrading one of the safety levels of the dosage (Brindha, S., et al., 2018). Previous studies on related Siddha and Ayurvedic formulations have suggested that while many herbal products are safe at therapeutic doses, improper processing or poor quality raw materials can lead to nephrotoxicity, hepatotoxicity or hematotoxicity (Stickel, F. 2015, Teschke, R., 2013). The World Health Organization (WHO) and national regulatory authorities have been advocating for comprehensive safety assessments of traditional medicines through standardized animal studies, including long-term toxicity protocols (WHO 2004).

Acute and sub-acute toxicity of Siddha herbal formulation Urai Mathirai given orally at doses of 10, 50 and 100 mg/kg.b.wt for 28 days did not show any toxic effect in Wistar rats. Therefore, the present study was conducted to evaluate the chronic toxicity of Siddha herbal formulation Urai Mathirai in experimental Wistar rats. Through this study the safety of this herbal medicine for clinical use of this traditional formulation in children for improving immunity can be established.

2. Material and Methods

2.1 Test animal

Wistar albino rats of both sex (Male and female) weighing about130–250 g were used in the chronic toxicology studies. The rats were housed in the Department of Pharmacology, Siddha central research institute, Chennai. The rats were kept in sanitized polypropylene cages housed with sterile corn cob as bedding materials at animal house, in an air conditioned environment with four rats in each cage and maintained at room temperature of (23 ± 2) ºC with relativehumidity (60% ± 10%) under 12-hour dark and light cycle (Bruckner, J.V., et al., 2001). Rats were given free access to standard pellet diet and water ad libitum(Nath, P et al., 2014). All experimental procedures were in compliance with the Committee for the Purpose of Control and Supervision of Experiments on animals (CPCSEA) and were approved by Institutional Animal Ethical Committee, with an approval number162/Pharma/SCRI/2017.

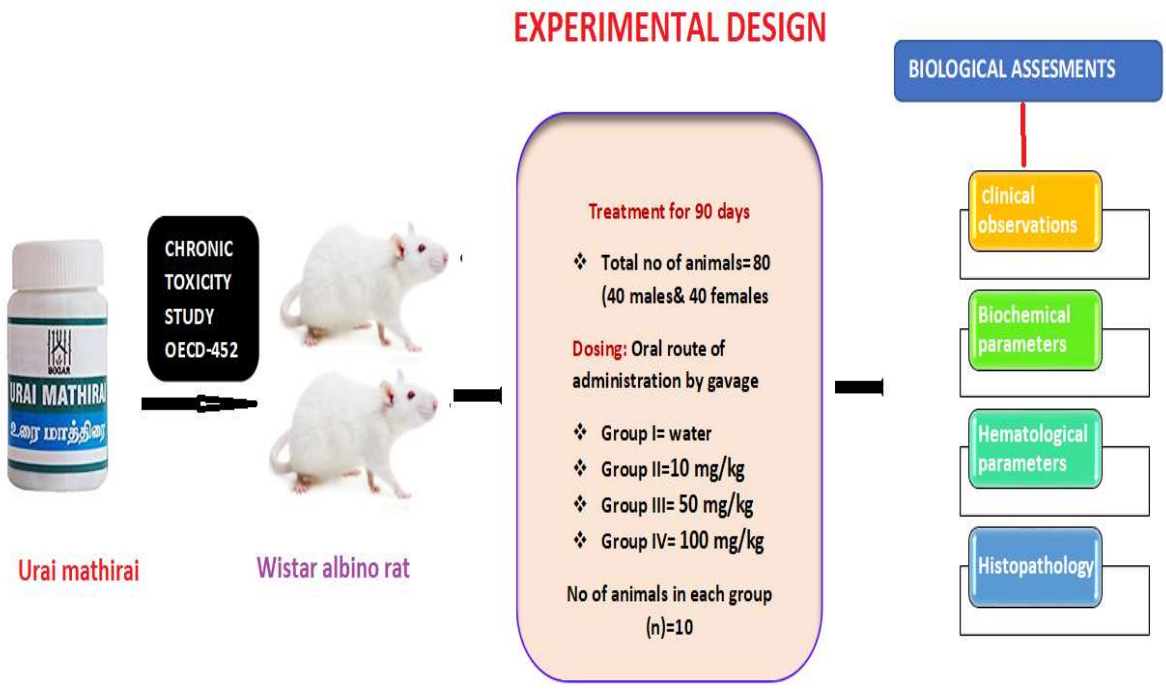
2.2 Dose calculation

The clinical dose of Urai mathirai in children is 50 mg (HED = 2.5mg/kg body weight). The animal (rat) doses are calculated as per the FDA guidelines and the calculated therapeutic dose (TD) was found to be 10mg/kg of body weight. In this study to determine the dose correlated effects, 5 times TD and 10 times TD i.e. 50 mg/kg & 100 mg/kg of bodyweight were chosen correspondingly(IPullaiah, C.P., et al., 2018).

2.3 Experimental design

The OECD Test Guideline 452 recommends 90-day or longer duration studies to evaluate toxicological endpoints such as biochemical, hematological, and histopathological alterations (No, O.T.,2018).Wistar albino Rats of both sexes (overnight fasting free access to water), aged 8–12 weeks' old were used. In 80 rats (40Male and 40females) were randomized into groups separately based on bodyweight. After the randomization process, each study animal was assigned a unique number and identified by a picric acid mark. Group-I served with vehicle as normal control, Group-II, Group-III and Group-IV administered with test drug orally at a dose of 10 mg/kg, 50 mg/kg and 100 mg/kg respectively for 90 days as shown in **figure 1**. Before drug administration, the body weight of each animal was determined and the dose was calculated according to the body weight for every week consecutively for 90 days (Sahu, M. et al., 2021). Rat general health, and signs of toxicity, body weight, mortality, food and water intake was monitored. At 90th day 50% of the experimental animals (40 animals form both sex) in each group were subjected to euthanasia. The necropsy was carried out on all euthanized animals and the organs were isolated and observed macroscopically for abnormalities. After 30days of post treatment the remaining half animals (40animals) were euthanized and organs were collected and observed macroscopically for abnormalities. The collected organs during the treatment and post treatment were preserved in 10% formaldehyde solution for histopathological examination(Gaddam, D.R; et al., 2020).

Figure 1: Experimental design of Urai mathirai- Siddha Herbal Formulation in wistar albino rats



2.3.1 Relative organ weight

The internal organs (brain, heart, thymus, lungs, liver, stomach, spleen, kidney, adrenal gland, pancreas and sex organs) excised from all the experimental rats after 90th day and 120th day. Organ-to-body weight ratio was calculated by dividing the weight (g) of each organ by the weight (g) of rats before sacrifice.

2.3.2 Biochemical parameters

The biochemical analysis was done on serum after centrifugation of collected blood and the following parameters like Blood glucose, Total Cholesterol, Triglyceride, HDL, LDL, SGOT, SGPT, ALP, GGT, Total Protein, Albumin, LDH, CRP, Creatinine Kinase levels, Creatinine Kinase – MB, Urea, Serum creatinine, Total Bilirubin, Uric acid, Serum Calcium were determined for both control and Urai mathirai treated groups by using standard biochemical method(Tiwari, V., et al., 2015).

2.3.3 Haematological parameters

The hematological parameters such as white blood cell (WBC), red blood cell (RBC), lymphocyte (LYMP), monocyte (MON), granulocyte (GRAN), hemoglobin (HGB), andHematocrit (Hct) Levels were evaluated(Tiwari, V., et al., 2015).

2.3.4 Histopathological examination

The organs (brain, heart, thymus, lungs, liver, stomach, spleen, kidney, adrenal gland, pancreas and sex organs) excised from all the experimental rats were fixed in 10% formalin in labeled bottles, and processed for histological examination. Tissues embedded in paraffin wax were sectioned 5 mm thick and stained with haematoxylin and eosin, mounted on glass slides and examined under a standard light microscope (de Picoli Souza, K., et al., 2016, Suttie, A.W.,et al., 2017).

2.4Statistical analysis

All the data was expressed as Mean ± SEM. Statistical analysis was tested by using One-way ANOVA followed by (Dunnett's test) using Graph pad prism version-8. The significance level was set at $P>0.05$ for all tests. Group II, III, and IV will be statistically compared with Group I to find the treatment related effects.

3. Results

3.1 Chronic toxicity study

All the treatment group ratswere administered with Urai mathirai drug solution at a dose of (10, 50 and 100mg/kg b.wt) throughout the 90 days found to be no clinical toxicity signs such as physical observations, behavioral changes and other parameters such as body weight, food intake, water intake, respiration, convulsion, tremor, changes in eye and skin colors, etc were observed in the treated group compared to the control group.

3.1.1Effect of Urai mathirai on relative organ body weight

The average and relative organ weight of Urai mathirai orally treated group of animals (at dose of 10, 50 and 100mg/kg b.wt) and control groups showed statistically non-significant differences ($P > 0.05$). The results revealed that, the internal organs of rats were not adversely affected throughout the treatment. The effect ofUrai mathirai on principal organ weights relative to body weight were presented in **Table 1.**

Table 1: Effect of Oral administration of *Urai mathirai* on Relative organs weight (g) of rats.

Organs	Group I (Normal)	Group II (10mg/kg b.w)	Group III (50mg/kg b.w)	Group IV (100mg/kg b.w)
Brain	6.88±1.11	7.14±0.59	6.58±0.58	7.17±0.49
Heart	3.90±3.73	3.81±0.72	3.75±0.12	3.80±0.45
Thymus	3.41±1.83	2.23±1.11	0.75±0.14	0.89±0.19
Lungs	7.53±0.47	6.61±0.36	7.01±0.44	7.88±1.22
Liver	39.60±4.11	34.43±1.46	36.04±1.32	39.06±5.04
Stomach	6.14±0.86	6.48±0.42	5.73±0.18	6.60±0.45
Spleen	2.42±0.18	2.91±0.29	2.94±0.16	2.56±0.47
Pancreas	1.64±0.95	3.30±0.36	4.35±1.64	3.19±0.38
Kidney	8.26±1.05	8.55±0.96	7.92±0.19	8.53±0.78
Adrenal gland	0.34±1.20	0.27±0.07	0.20±0.04	0.22±0.05

All values are expressed as mean ± SEM (n=8). No significant difference since $p > 0.05$, as compared to control group.

3.1.2Effect of Urai mathirai on biochemical parameters

The results of the various biochemical parameters on the experimentally treated rats with the oral administration of the Urai mathirai at a dose of (10, 50 and 100mg/kg b.wt) and normal groups showed statistically non-significant differences ($P > 0.05$). The results revealed that no abnormal changes in serum biochemical parameters such as albumin, total protein, globulin, Total bilirubin, urea, sodium, creatinine and uric acid levels etc., when compared to control group. The effect of Urai mathirai on biochemical parameters measured and summarized in **Table 2.**

Table 2 Effect of oral administration *Urai mathirai* on biochemical parameters at the end of the treatment period

Organs	Group I (Normal)	Group II (10mg/kg b.w)	Group III (50mg/kg b.w)	Group IV (100mg/kg b.w)
Blood glucose(mg/dl)	72.47±6.83	71.00±5.97	75.36±6.88	72.71±6.12
Total Cholesterol levels (mg/dl)	73.13±3.78	71.64±3.04	68.86±4.49	70.65±3.57
Triglyceride levels (mg/dl)	103.00±10.05	121.64±14.94	109.93±9.90	101.29±13.96
HDL levels (mg/dl)	30.87±6.70	25.07±1.41	25.36±1.76	23.47±1.26
LDL levels (mg/dl)	28.27±3.65	23.00±3.36	21.43±3.41	27.56±2.89
SGOT levels (U/L)	164.40±12.31	190.43±14.45	194.29±12.72	162.53±4.64
SGPT levels (U/L)	62.60±2.07	64.79±4.10	64.50±3.17	67.76±9.74
ALP levels (U/L)	200.60±19.15	183.21±16.86	220.36±20.74	165.47±14.62
GGT levels (U/L)	4.60±0.46	4.92±0.47	4.64±0.37	4.71±0.32
Total Protein levels (g/dl)	7.67±0.11	7.50±0.10	7.59±0.17	7.64±0.18
Albumin levels (g/dl)	3.41±0.07	3.44±0.10	3.37±0.13	3.45±0.06
LDH levels (U/L)	1234.13±65.36	1184.50±82.60	1232.50±91.74	14090.12±18.76
CRP levels (mg/L)	0.48±0.06	0.54±0.09	0.50±0.08	0.58±0.11
Creatinine Kinase levels (U/L)	814.87±70.65	904.79±124.68	887.07±139.57	651.65±41.45
Creatinine Kinase – MB levels (U/L)	507.80±43.57	496.50±50.51	446.14±36.92	369.76±18.04
Urea levels (mg/dl)	30.67±1.68	32.57±2.26	32.57±1.25	34.71±1.57
Serum creatinine levels (mg/dl)	0.53±0.02	0.53±0.02	0.56±0.02	0.54±0.03
Total Bilirubin levels (mg/dl)	0.12±0.01	0.11±0.01	0.11±0.01	0.10±0.00
Uric acid levels (mg/dl)	0.13±0.02	0.12±0.01	0.13±0.02	0.12±0.01
Serum Calcium levels (mg/dl)	9.98±0.12	9.89±0.12	9.12±0.68	14.22±4.49

All values are expressed as mean ± SEM (n=15, 14, 15,17). No significant difference since $p > 0.05$, as compared to control group.

3.1.3Effect of Urai mathirai on Hematological parameters

The hematological parameters white blood cell (WBC), red blood cell (RBC), lymphocyte (LYMP), monocyte (MON), granulocyte (GRAN), hemoglobin (HGB), andHematocrit (Hct) Levelswere within normal limits compared to control group. No significant differences ($P > 0.05$) between treated animals with the Urai mathirai orally at dose of 10 mg/kg, 50 mg/kg and 100 mg/kg and control group rats were found. The hematological parameters were measured and summarized in **Table 3**.

Table 3: Effect of oral *Urai mathirai* on haematological parameters at the end of the treatment period

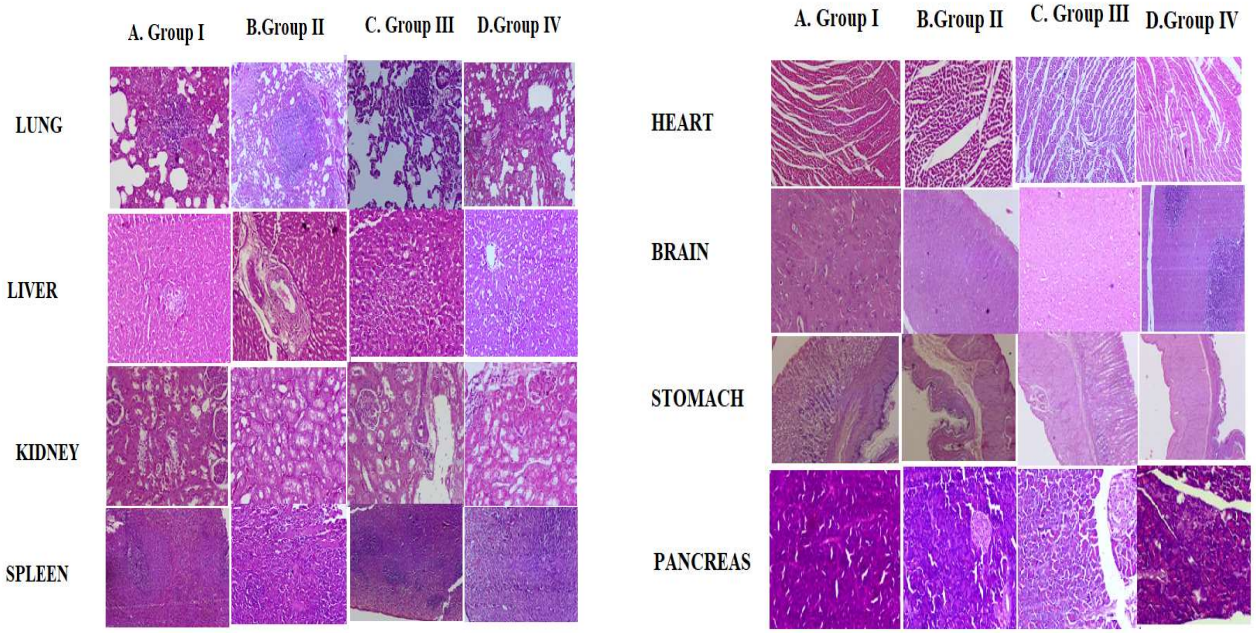
Parameters	Group I (Normal)	Group II (10 mg/kg b.w)	Group III (50 mg/kg b.w)	Group IV (10 mg/kg b.w)
WBC (10^9/L)	12.10±0.64	11.59±*0.99*	*10.94±0.71*	*10.52±0.80*
RBC (10^{12}/L)	7.42±0.17	7.78±*0.31*	*7.66±0.21*	*7.76±0.24*
LYMP (10^9/L)	8.13±*0.40*	9.36±*1.10*	*7.54±0.55*	*7.11±0.55*
MON (10^9/L)	0.31±*0.02*	0.31±*0.03*	*0.32±0.03*	*0.31±0.03*
GRAN (10^9/L)	3.68±*0.28*	3.21±*0.38*	*3.08±0.24*	*2.81±0.29*
HGB (g/dL)	12.00±*0.27*	12.44±*0.47*	*12.19±0.26*	*19.61±7.41*
HCT (%)	38.44±*0.87*	39.36±*1.56*	*38.17±0.87*	*39.32±1.37*

All values are expressed as mean ± SEM (n=13, 14,15,17).No significant difference since $p > 0.05$, as compared to control group, except $p < 0.05$ in group

3.1.4Effect of Urai mathirai in Histopathological Study

Sections of lung, liver, kidney, spleen, heart, and brain tissues were perfused with 10% formalin and stored in the same and used for histopathological studies. The tissues were then embedded in molten paraffin wax. Sections were cut at 5µm thickness and stained with haematoxylin and eosin. The sections were then viewed under light microscope. The macroscopic examination of organs of treated rats revealed no abnormalities in the colour or texture when compared with the organs of the control group. Although some differences have been observed in the histopathological slides were presented in**Figure 2**.Histopathological findings of lungs showed mild pulmonary oedema, multi focal mild mononuclear cell infiltration in peribronchiolar and alveolar region of control rats (Group I) and also treated rat's groups (Group II to Group IV) of Urai mathirai orally at a dose level of10 mg/kg, 50 mg/kg and 100 mg/kg).It revealed that no significant changes were observed related to drug toxicity effect.Histopathological findings of liver showed sinusoidal congestion, very mild hepatocellular degeneration and focal hepatocellular necrosis in both control rats (Group I) and also in treated rats groups (Group II to Group IV) of Urai mathirai orally at a dose level of (10 mg/kg, 50 mg/kg and 100 mg/kg). It revealed that no significant changes were observed related to drug toxicity. Histopathological findings of kidney showed mild tubular epithelial cell degeneration and focal mild interstitial mononuclear cell infiltration in both control rats (Group I) and also in treated rats groups (Group II to Group IV) of Urai mathirai orally at a dose level of(10 mg/kg, 50 mg/kg and 100 mg/kg).It revealed that no significant changes were observed related to drug toxicity effect. Histopathological findingsof spleen showed no abnormality in both control rats and also in treated rats groups (Group II to Group IV) ofUrai mathirai orally at a dose level of(10 mg/kg, 50 mg/kg and 100 mg/kg). It revealed that no significant changes were observed related to drug toxicity effect. Heart showed no abnormality in both control rats and also in treated rats groups (Group II to Group IV) ofUrai mathirai orally at a dose level of(10 mg/kg, 50 mg/kg and 100 mg/kg).It revealed that no significant changes were observed related to drug toxicity effect. brain showed no abnormality in both control rats and also in treated rats groups (Group II to Group IV) ofUrai mathirai orally at a dose level of(10 mg/kg, 50 mg/kg and 100 mg/kg).It revealed that no significant changes were observed related to drug toxicity effect. Histopathological findings of glandular and non-glandular stomach showed no abnormality in both control rats and also in treated rats groups (Group II to Group IV) of Urai mathirai orally at a dose level of (10 mg/kg, 50 mg/kg and 100 mg/kg). It revealed that no significant changes were observed related to drug toxicity effect. Pancreas showed no abnormality in both control rats and also in treated rats groups (Group II to Group IV) ofUrai mathirai orally at a dose level of (10 mg/kg, 50 mg/kg and 100 mg/kg). It revealed thatno significant changes were observed related to drug toxicity effect.

Figure 2: (A-D) Histopathological findings of Lung, Liver, Kidney, Spleen, Heart, Brain, Stomach and Pancreas in different groups of rats.



4. Discussion

Chronic toxicity evaluation of Urai Mathirai for 90 days in Wistar albino rats showed no adverse effects on general health, growth or organ function. These results are consistent with the historical and empirical evidence of its safe use in traditional Siddha medicine. Serum markers for liver (SGOT, SGPT, ALP, total bilirubin) and kidney (urea, creatinine) functions remained within normal ranges in all dose groups. This indicates that the formulation does not induce hepatocellular damage or impair renal filtration capacity even after chronic administration. No significant changes were observed in hemoglobin, RBC, WBC, platelet count or hematocrit values, indicating that the formulation does not interfere with hematopoiesis or induce anemia or leukocytosis. These results are consistent with previous safety evaluations of Siddha formulations. Histological analysis of vital organs (liver, kidneys, heart, lungs, spleen and stomach) did not reveal any structural changes, inflammation, necrosis or fibrosis in the treated animals. The absence of pathological lesions confirms the biochemical findings and supports the non-toxic nature of the formulation under chronic conditions.

The absence of systemic or organ-specific toxicity confirms the traditional safety claims associated with Urai Mathirai. The protective pharmacological effects of its herbal constituents such as the antioxidant and hepatoprotective activities of Zingiber officinale and Piper longum contribute to the observed safety (Roy, S. 2017, Stickel, F 2015).

4. Conclusion

Urai mathirai administered in 3 doses by oral route (at therapeutic dose of 10 mg/kg, average dose 50 mg/kg and high dose 100mg/kg) regularly for 90 days did not produce any toxicity in animal models. There were no statistically significant alterations found in behavior, biochemistry, hematological parameters, organ weight and histopathology during the experimental period.

Availability of data

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available to privacy or ethical restrictions.

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Conflict of interest

All the authors declare that have no conflict of interest in this manuscript.

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References

- Bigoniya, P., Sahu, T. and Tiwari, V., 2015. Hematological and biochemical effects of sub-chronic artesunate exposure in rats. *Toxicology reports*, *2*, pp.280-288.**DOI: 10.1016/j.toxrep.2015.01.007**
- Devi, M.R., Reddy, G.D., Kumar, P.N., Sathiyarajeswaran, P. and Elankani, P., 2019. Herbomineral formulations safety and efficacy employed in siddha system of medicine: A Review. *Int. Res. J. Pharm*, *10*(1), pp.16-24.**DOI:10.7897/2230-8407.10014**
- Gaddam, D.R., Sathiyarajeswaran, P., Patturayan, R., Ganesan, R., GV, N.K., Pullaiah, C.P. and DHANARAJ, K., 2020. Evaluation of Chronic toxicity of Urai mathirai-Siddha Herbal Formulation. *Authorea Preprints*.**DOI: 10.22541/au.158765852.23761913**
- Geneva, S., 2004. WHO Guide lines on Safety Monitoring of Herbal Medicines in Pharmacovigilance Systems.[Google Scholar].
- Lopes, R.H.O., Macorini, L.F.B., Antunes, K.Á., Espindola, P.P.D.T., Alfredo, T.M., Rocha, P.D.S.D., Pereira, Z.V., Santos, E.L.D. and de Picoli Souza, K., 2016. Antioxidant and hypolipidemic activity of the hydroethanolic extract of Curatella americana L. leaves. *Oxidative medicine and cellular longevity*, *2016*(1), p.9681425.**https://doi.org/10.1155/2016/9681425**
- Muralidhara, S., Ramanathan, R., Mehta, S.M., Lash, L.H., Acosta, D. and Bruckner, J.V., 2001. Acute, subacute, and subchronic oral toxicity studies of 1, 1-dichloroethane in rats: application to risk evaluation. Toxicological sciences, 64(1), pp.135-145.**DOI: 10.1093/toxsci/64.1.135**
- Minnady, M., Jayapal, G., Poochi, S., Nethaji, P. and Mathalaimuthu, B., 2022. Hepatoprotective Effect of Indigenous Medicinal Plants: A Review. *Indian Journal of Pharmaceutical Sciences*, *84*(5).
- Nath, P. and Yadav, A.K., 2014. Acute and sub-acute oral toxicity assessment of the methanolic extract from leaves of Hibiscus rosa-sinensis L. in mice. *Journal of intercultural ethnopharmacology*, *4*(1), p.70.**DOI: 10.5455/jice.20141028021746**
- Nakaphan, T., Teerachaisakul, M., Sawanyawisuth, K., and Pongpirul, K. (2025). Herbal Product Availability and Consumption Patterns: A Comprehensive Scoping Review. Natural Resources for Human Health, 5(4), pp.522-531. DOI: https://doi.org/10.53365/nrfhh/204973
- No, O.T., 2018. 452: Chronic toxicity studies. *OECD Guidelines for the testing of chemicals, Section*, *4*.
- Patwardhan, B., Warude, D., Pushpangadan, P. and Bhatt, N., 2005. Ayurveda and traditional Chinese medicine: a comparative overview. *Evidence-Based Complementary and Alternative Medicine*, *2*(4), pp.465-473.

- Roy, S. and Awasthi, H., 2017. Herbal medicines as neuroprotective agent: A mechanistic approach. Int J Pharm Pharm Sci, 9(11), pp.1-7. DOI: https://doi.org/10.22159/ijpps.2017v9i11.19444
- Sahu, M., Tiwari, R.K., Sharma, V., Shukla, S.S. and Pandey, R.K., 2021. Evaluation of toxicity and antiasthmatic potential of an ayurvedic formulation on experimental animals. *Indian Drugs*, *58*(2). **DOI :**10.53879/id.58.02.12315
- Sathiyarajeswaran, P., Shree Devi, M.S., Sunil Kumar, K.N., MuthuTamizh, M., Satheesh, D. and Brindha, S., 2018. Quality Standards for UraiMathirai-A Siddha Immunomodulator Formulation for Children. *The Journal of Phytopharmacology*, *7*(1), pp.40-44.**DOI:10.31254/phyto.2018.7109**
- Sathiyarajeswaran, P., Pattarayan, R., Reddy, G.D., Kumar, G.V.N. and Pullaiah, C.P., 2018. Experimental evaluation of analgesic and anti-inflammatory potential of Urai mathirai-a Siddha formulation.**http://www.jgtps.com/admin/uploads/X017Gs.pdf**
- Suttie, A.W., Boorman, G.A., Leininger, J.R., Eustis, S.L., Elwell, M.R., MacKenzie, W.F. and Bradley, A. eds., 2017. *Boorman's pathology of the rat: Reference and atlas*. Academic Press.
- Stickel, F. and Shouval, D., 2015. Hepatotoxicity of herbal and dietary supplements: an update. *Archives of toxicology*, *89*(6), pp.851-865.**https://doi.org/10.1007/s00204-015-1471-3**
- Teschke, R., Frenzel, C., Schulze, J. and Eickhoff, A., 2013. Herbal hepatotoxicity: challenges and pitfalls of causality assessment methods. *World Journal of Gastroenterology: WJG*, *19*(19), p.2864. doi: 10.3748/wjg.v19.i19.2864