EVALUATION OF HEPATOTOXICITY OF "*SINNA SIVAPPU MAATHIRAI*": A SIDDHA HERBO MINERAL DRUG, IN PATIENTS WITH RESPIRATORY DISEASES WHO VISIT SIDDHA TEACHING HOSPITAL KAITHADY, JAFFNA

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Introduction

Siddha medical system has been practiced by Tamil speaking community in South part of India and North East part of Sri Lanka. *Sinna Sivappu Maathirai* (SSM) is a compound herbo-mineral Siddha drug. It is prepared by nine raw materials of herbs, one salt as Borax/ Sodium Bi Borate and a mineral, red sulphide of mercury. SSM is currently prescribed for cough;, breathing difficulties, cough with fever and chest pain while cough. "Ayurveda and Siddha products offer very little data on toxicological profile and more stringent toxicological requirements of these product as required by prominent regulatory agencies are still unmet" (1). A discussion on the use of heavy metals in herbal formulations and their safety was initiated by WHO with contribution of the regional experts of the field. Many participants of the discussion felt that any change of formulation or indication of a traditional medicine required safety studies, even if manufactured according to classical texts. So far, limited studies have been published on herbo-mineral preparations using in Sri Lankan Siddha medical system. According to the information, large quantity of SSM used widely per annum in Northern Provincial hospitals and Siddha teaching hospital since 2006. However, no report is available on safety evaluation of usage of SSM. Hence the present study designed to evaluate the hepatotoxicity of SSM in patients.

Materials and Methods

Study Drug – Sinna Sivappu Maathirai

The drug is prepared as *Kuntriyalavu* according to the standard protocol in classical text of *Suthesa Vaithya Oudatha Thiraddu*. The pharmacy in Siddha teaching hospital Kaithady, prepare SSM accordingly and it is using to treat patients in the hospital. The drug has been prescribed as two doses of *Kuntriyalavu* two times a day after meals with *anupanm* of 5 ml betel extract. Siddha texts (2) mentioned that one *Kuntriyalavu* is equivalent to 130mg. The SSM is prescribed for the duration of 7 days. All raw materials including *Sathilingam (Redsulphide of Mercury)* used to prepare SSM are authenticated

and supplied by technical evaluation committee of the department of Ayurveda.

It was a descriptive observational study. Study carried out at Siddha Teaching Hospital, Kaithady, Jaffna, Sri Lanka. Study participants were patients prescribed with SSM for the treatment of respiratory symptoms (the patients treated for cough with phlegm, chest pain while cough and breathing difficulty) at Siddha Teaching Hospital, Kaithady. Patients who prescribed SSM for the first time included for the study. Children below 12years, pregnant women, and mentally incompetent patients, patients with hepatic and renal impairment were excluded.

According to Stephen *et al.* (2007) sample size was calculated. Maximum sample was 64. Structured interviewer administered questionnaire and investigation were performed by the researcher in the laboratory at Department of Biochemistry, Faculty of Medicine, University of Jaffna. Aspartate amino transferase (AST) and alanine amino transferase (ALT), bilirubin and ALP *(Alkaline Phosphatase)* were investigated to evaluate the hepato-toxicity. Pretest was done in 05 patients who presented to the Rural Siddha hospital Kodikamam for validation of the questionnaire. These patients were not included in the main study. After obtaining written informed consent, patients were recruited for the study till the desired sample size reached (Purposive sampling). Ethical clearance was obtained from Ethical Review Committee, Faculty of Medicine University of Jaffna Sri Lanka.

Data collection

After obtaining consent, the patients were recruited for the study and the detail medical history of the selected patients was taken through the structured interviewer administered questionnaire. All the patients were assessed at baseline and after 1st week, 2nd week, 4th week and 12th week after completing one week treatment. All the data collection was performed at OPD of Siddha Teaching Hospital Kaithady.

Collection of blood

Before collecting blood, the participants were informed and obtained written consent for withdrawing blood. Nursing officer from Siddha Teaching Hospital Kaithady collected blood. The laboratory at Siddha Teaching Hospital was used with the permission of Medical officer in-charge of the hospital. Blood samples (5 ml from each patient) were collected by venipuncture and stored in appropriate containers. Each blood sample was given an identity number based on the serial number of questionnaire and data record. Samples transported to Department of Biochemistry Faculty Medicine, University of Jaffna in an ice box (4^0c) within 4 hours and lab procedures continued. After completion of Laboratory investigation, the sample disposed by incineration.

Data analysis

Mean, standard deviation, percentile paired T-test and correlation of coefficient were calculated using SPSS 22.

Result and Discussion

Table 1. Gender based AST (U/L) distribution, mean difference (MD) and its significant level

Assessment	AST (U/L) - Male (41)							AST (U/L) - Female (23)						
	Mean	±	SD	MD	±	SD	Sig.	Mean	±	SD	MD	±	SD	Sig.
BL	23.18	±	9.7					19.3	±	1.29				
FW1	23.76	±	9.7	-0.6	±	5.95	0.53	18.61	±	1.19	0.7	±	1.81	0.08
FW2	23.27	±	9.5	-0.1	±	6.54	0.93	18.25	±	1.09	1.06	±	3.49	0.16
FW3	23.59	±	12	-0.4	±	8.97	0.77	18.29	±	1.31	1.01	±	6.69	0.47
FW4	22.33	±	9.9	0.85	±	8.53	0.53	19.46	±	1.85	-0.16	±	9.77	0.94

Cut-of value of AST (>37 U/L for male and >31 U/L for female) (3), SD – Standard Deviation; B/L – Baseline, FW1 - Follow up 1(Completion of first week), FW2 - Follow up 2 (Completion of second week),

AST values observed in the subjects at baseline and follow ups were in normal range according to the standard reference. MD (Mean difference) between base line and follow-up levels of were statistically not significant in males as well females. Same as in the standard reference, gender based distribution of AST was lower in females than males.

Table 2. Gender based ALT (U/L) distribution & mean difference and it's significant

Assessment	ALT (U/L) - Male (41)							ALT (U/L) - Female (23)						
	Mean	±	SD	MD	±	SD	Sig.	Mean	±	SD	MD	±	SD	Sig.
BL	28.28	±	16.81					14.16	±	9.77				
FW1	30.24	±	19.18	-1.97	±	10.1	0.22	14.01	±	8.69	0.14	±	3.69	0.85
FW2	29.06	±	16.99	-0.78	±	6.69	0.46	13.97	±	7.95	0.19	±	5.39	0.87
FW3	29.69	±	21.00	-1.41	±	11.3	0.43	13.38	±	4.84	0.78	±	7.68	0.63
FW4	27.83	±	18.15	0.45	±	9.41	0.76	14.39	±	7.31	-0.2	±	4.81	0.82

Cut-of value of ALT (>40 U/L for male and >31 U/L for female) (3)

ALT values observed in the subjects at baseline and follow ups were in normal range according to the standard reference. MD (Mean difference) between base line and follow-up levels of were statistically not significant in males as well females. Same as in the standard reference, gender based distribution of ALT was lower in females than males.

Table 3. Bilirubin (mg/dl) level between base line and follow-ups in different age categories

Age Range (years)	Bilirubin levels (mg/dl) in the baseline and follow-ups																	
	BL				FW1			FW2			FW3			FW4				
	N	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD	Mean	±	SD		
18-28	19	1.44	±	0.87	1.40	±	0.54	1.31	±	0.48	1.19	±	0.5	1.23	±	0.48		
29-38	16	1.38	±	0.55	1.36	±	0.51	1.43	±	0.56	1.34	±	0.4	1.16	±	0.38		
39-48	16	1.18	±	0.99	0.71	±	0.15	1.00	±	0.65	0.87	±	0.3	0.80	±	0.14		
49-58	8	1.55	±	1.01	1.25	±	0.79	1.30	±	0.78	1.22	±	0.7	1.08	±	0.44		
59-68	12	0.77	±	0.27	0.79	±	0.27	0.78	±	0.29	0.86	±	0.3	0.85	±	0.23		
69-78	1	2.03	±	0.00	1.47	±	0.00	1.50	±	0.00	1.5	±	0	2.17	±	0		
≥ 18	**64**	**1.29**	**±**	**2.78**	**1.17**	**±**	**0.56**	**1.20**	**±**	**0.57**	**1.13**	**±**	**0.5**	**1.08**	**±**	**0.42**		

Reference value Adult: 0.17-1 mg/dl (4)

Table 4. Mean difference and its Significant Bilirubin level (mg/dl) between baseline and follow-ups

	Bilirubin (mg/dl)			
Assessments	**MD**	**±**	**SD**	**Sig.**
BL-FW1	0.12	±	0.77	0.22
BL-FW2	0.09	±	0.72	0.33
BL-FW3	0.16	±	0.69	0.07
BL-FW4	0.21	±	0.72	0.02

Serum bilirubin concentration in the subjects at the baseline as well as follow ups were higher than normal range according to the standard reference. There was no significant difference (P-value < 0.05) between the mean difference between baseline and follow ups except 4th follow-up.

Table 5. ALP (IU/L) level between baseline and follow-ups in different age

Age Group	ALP levels (IU/L) at baseline and follow-ups																	
	BL				FW1			FW2			FW3			FW4				
	N	Mean		SD	Mean		SD	Mean		SD	Mean		SD	Mean		SD		
18-28	19	175.54	±	43.34	167.47	±	40.83	168.0	±	38.86	171.18	±	39.6	167.00	±	39.48		
29-38	16	161.54	±	40.83	160.65	±	38.34	162.2	±	44.33	161.31	±	39.78	152.85	±	28.04		
39-48	16	143.54	±	23.29	158.83	±	16.55	149.7	±	17.77	152.38	±	20.47	160.79	±	19.01		
49-58	8	176.63	±	37.78	175.29	±	33.10	172.9	±	26.5	168.92	±	21.56	179.25	±	35.25		
59-68	12	176.89	±	44.13	177.42	±	39.61	178.8	±	40.36	176.31	±	44.22	180.97	±	39.72		
69-78	1	207.00	±	00.00	207.00	±	00.00	204.0	±	00.00	182.00	±	00.00	217.00	±	00.00		
≥ 18	**64**	**168.92**	**±**	**40.55**	**168.15**	**±**	**36.39**	**167.47**	**±**	**37.33**	**167.21**	**±**	**36.41**	**167.62**	**±**	**35.18**		

ALP range: 98-279 IU/L (5)

Table 6. Mean difference and its Significant of ALP (IU/L) Between baseline and follow-ups

ALP (IU/L)				
Assessments	MD	±	SD	Sig.
BL-FW1	0.78	±	18.6	0.74
BL-FW2	1.45	±	19.4	0.55
BL-FW3	1.71	±	19.4	0.48
BL-FW4	1.30	±	24.1	0.67

ALP values observed in the subjects at baseline and follow ups were in normal range according to the standard reference. In this study, same as in the standard reference, aged based distribution of ALP was lower in 18 and above years. MD (Mean difference) between base line and follow-up levels of were statistically not significant among the age groups. The result showed that the AST, ALT, ALP and bilirubin were not significantly increased by using SSM for one week continuously.

Conclusion and Recommendation

According to the results, one week treatment of SSM showed no hepatotoxicity in treated patients. Therefore, SSM can be recommended to use for a week period to treat respiratory symptoms in adults above 18 years old.

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