INTERNATIONAL JOURNAL OF CURRENT RESEARCH IN BIOLOGY AND MEDICINE
ISSN: 2455-944X
www.darshanpublishers.com
Volume 4, Issue 10 - 2019

Original Research Article

DOI: http://dx.doi.org/10.22192/ijcrbm.2019.04.10.001

Preclinical Safety Evaluation of Sarabendira Siddha Maruthuva Sudar Chooranam by Acute and Subacute repeated oral toxicity Studies in Rodents

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Abstract

Siddha system of medicine is flourishing across the world as it depicted with the physiology od rejuvenation and cure in altering the human physiology under diseased condition. The use of traditional herbal medicines and phytonutrients or nutraceuticals continues to expand rapidly across the world with many people now resorting to these products for treatment of various health challenges in different national healthcare settings. It is estimated that up to four billion people (representing 80% of the world's population) living in the developing world rely on herbal medicinal products as a primary source of healthcare and traditional medical practice which involves the use of herbs is viewed as an integral part of the culture in those communities. As per the literature formulation like sarabendira siddha maruthuva sudar chooranam (SBSMSC) has potential of rejuvenate, replenish and restore the disrupted physiology to the normal. In the acute study, a single dose of 5000 mg/kg was orally administered and experimental animals were monitored for 14 days. In the sub-acute study, repeated doses (500 and 1000 mg/kg/day) of the test drug SBSMSC were administered for 28 days and biochemical, hematological and histopathological parameters were evaluated. Results of acute toxicity study revealed that the drug SBSMSC was found to be non-toxic at a dose of 5000 mg/kg b.w. In the sub-acute toxicity study there is no significant variations in body weight, hematological and biochemical parameters were observed in the experimental groups at the dose of 500 and 1000 mg/kg with no mortality in both male and female rats subjected to the study. Histopathological studies revealed no alteration in organ morphology and cyto architecture of vital organs like heart, brain, kidney, liver, spleen, reproductive organs etc. In conclusion the results of the acute and sub-acute toxicity study clearly demonstrate that the formulation SBSMSC was safe and long-term administration of drug may not claim any adverse event.

Keywords: Sarabendira siddha maruthuva sudar chooranam, Siddha, Acute, Sub-acute toxicity, Hematological, Rejuvenation

1. Introduction

Medicinal plants have been used for health and disease management globally. The use of these plants in health care delivery especially in resource poor settings is increasing. About eighty percent of the world's population depend on traditional medicine for primary health care [1,2]. Even though the use of these plants has shown promising potential with high global demand, there are still concerns about not only their use but also their safety [3].

Many traditional and complementary medicine practitioners often refute the WHO certification scheme to regulate the quality of medicinal products [4]. This explains why there exist divergent opinions on the various applications of medicinal herbs [5]. Also, this constitutes a setback against the scientific justification of folklore medicines applications [6,7]. In order to ensure safety, the scientific community has birthed three notions. Firstly, there must be a study to show safety profiles of any compound/product that is claimed to be beneficial to a living organism. The second is to assess the chemical constituents of the traditional medicinal agent. And lastly is to set the guidelines to investigate the proposed folklore application which is a step towards drug development and discovery. Thus, every medicinal plant or product is being sought for, regarding the verification for public acceptance and consequently the necessity of toxicological reports [8].

Herbal formulations are usually regarded as safe or of low toxicity based on their long history of use by humans [9]. Nevertheless, according to the recent survey indicated that many of these products used in traditional medicine showed adverse effects [10].

Siddha system of medicine majorly relies on ancient traditional preparations for treating several infectious and non-communicable diseases. As per the vedic literature it has been provoked that this method of treatment has emerged from southern region of India and progressed though out the world [11]. Sarabendira siddha maruthuva sudar chooranam composed of several bioactive herbal components with synergistic pharmacological activity as per the siddha literatures. Since safety continues to be a major issue with the use of medicinal plants, it is important to conduct toxicity studies on them to ascertain their safety profile. Therefore, evaluating the toxicological effects of any herbal preparations intended to be used in animals or humans is an important aspect of its assessment for potential toxic effects. The main aim of the present study is to evaluate the safety profile of the siddha drug SBSMSC through short term (acute) and long term (sub-acute) toxicity studies in accordance with OECD (Organization for economic co-operation and development) guideline.

2. Materials and Methods

2.1.Animal

Healthy adult Wistar albino rats were used for the study. The animals were housed in poly propylene cages and were kept in well ventilated with 100% fresh air supported by air handling unit (AHU). A 12 light / dark cycle were maintained. Room temperature was maintained between 22 ± 2˚Cand relative humidity 50–65%. They were provided with standard pelleted feed and water *ad libitum*. All the animals were acclimatized to the laboratory for 7 days prior to the start of the study. The experimental protocol was approved by The Institutional Animal Ethics Committee of Sathyabama Institute of Science and technology, Chennai, Tamil Nadu, India with the IAEC approval number: SU/CLATR/IAEC/X/088/2018

2.2. Acute toxicity Study

The animals were fasted overnight (08- 12 hrs) with free access to water. Study was conducted with single oral administration of study drug Sarabendira siddha maruthuva sudar chooranam (SBSMSC) at the dose of 5000mg/kg (p.o) to experimental rats. The animals were observed continuously for first 72 h and then 14 days for emerging signs of behavioral changes, body weight changes and for mortality.

Occurrence of toxicity in animals were observed continuously for the first 4 to 24 h and observed periodically for the next 14 days. Observation includes the change in skin, fur, eyes and mucus membrane. Appearance of C.N.S,C.V.S and A.N.S related toxicity such as tremors, convulsions, sedation, steric behavior, respiratory distress, cardiovascular collapse, response to sensory stimuli, salivation, diarrhea, lethargy, sleep, coma and mortality were observed with special attention [12].Body weight was recorded periodically. At the end of the experiment all animals were subjected to gross necropsy and observed for pathological changes.

2.3. Sub-Acute toxicity Study

Animals were allowed acclimatization period of 7 days to laboratory conditions prior to the start of treatment. The female rats used for the study were nulliparous and non-pregnant. The animals were randomly divided into control group and drug treated groups of 18 wistar albino rats (09 males and 09 females) were selected and divided into three groups. Each group consist of 06 animals (03 Males and 03 Females). First group served as a control and other two groups were treated with test drug SBSMSC (500 and 1000 mg/kg/day) for 28 days.

The rats were weighed periodically and observed for signs of toxicity pertains to C.N.S, C.V.S, A.N.S including behavioral changes, food - water intake and morphological changes. At the end of 28^{th} day, the animals were fasted for overnight with free access to water. On 29^{th} day the animals were sacrificed with excess dose of anesthesia as listed in the CPCSEA annexure. Blood samples were collected from aorta and stored in EDTA (ethylenediamine –tetra acetate) for Hematological analysis and for serum generation for biochemical analysis. The vital organs were harvested and carefully examined for gross lesions. The organs were preserved in 10% formalin for histopathological assessment and interpretation [13].

2.4. Hematological analysis

Blood samples were analyzed using established procedures using automated mindray hematology analyzer 2800. Parameters evaluated includes Packed Cell Volume (PCV), Red Blood Cells (RBC) count, White blood cell count (WBC), Platelet Count, Hemoglobin (Hb), Mean cell Haemoglobin Concentration (MCHC), Mean Red Cell Volume (MCV), Mean Cell Hemoglobin (MCH), Mean platelet volume (MPV), Neutrophils, Eosinophil's, Basophils, Lymphocytes and Monocytes.

2.5. Biochemical analysis [14]

Serum samples were analyzed for High Density Lipoprotein (HDL), Low density Lipoprotein (LDL), Very low density Lipoprotein (VLDL), Triglycerides (TGL), Total Cholesterol, Blood urea nitrogen (BUN), Creatinine, Albumin, Total Protein, Glucose, Uric acid, Aspartate Transaminase (AST), Alanine amino Transaminase (ALT) and Alkaline Phosphatase (ALP) using Mind ray auto analyzer model BS 120.

2.6. Histopathological evaluation [15]

Vital organs were harvested and the histological slides of organs were made and observed under the microscope. The pathological observations of cross section of these organs were performed on gross and microscopic analysis. Histological examinations were performed on the preserved tissues with particular emphasis on those which showed gross pathological changes.

2.7. Statistical analysis[16]

The statistical analysis will be carried by one-way ANOVA (GRAPH PAD PRISM 5 computer program). Results were expressed as mean ± standard error. A statistical comparison was carried out using the Dunnet's test for the control and treatment group. P-values less than 0.05 were set as the level of significance.

3. Results

3.1. Assessment of clinical signs in rats treated with SBSMSC on Acute toxicity study

The dose of SBSMSC used for acute toxicity study is 5000mg/kg is higher than the normal therapeutic dose. No mortality observed at this dose level, further no significant change with respect to clinical signs on acute toxicity observed for (24-48 h) and a long period (14 days). The results were tabulated in Table 1.

Table 1: Clinical signs in rats on Acute toxicity study

Clinical Signs Parameters for the duration of 14 days	Test Drug 5000mg/ Kg
Lacrimation	Absence
Salivation	Absence
Animal appearance	Normal
Tonic Movement	Absence
Clonic Movement	Absence
Laxative action	Absence
Touch Response	Normal
Response to Sound	Normal Response
Response to Light	Normal Response
Mobility	Normal Response
Respiratory Distress	Nil
Skin Color	Normal
Stereotype behavior	Absence
Piloerection	Absence
Limb Paralysis	Absence
Posture	Normal
Open field behavior	Normal
Giat Balancing	Normal
Freezing Behaviour	Absent
Sings of Stress and Anxiety	None Observed
Muscular coordination	Normal
Muscle grip	Normal
Sedation	Absence
Social Behavior	Normal
Urine Analysis	No Abnormality
Urine Colour	Yellowish
Urine pH	6
Urine -Glucose	Absence
Urine -Ketones	Absence
Urine- Bilirubin	Absence
Urine-Blood Cells	Negative
Urine - Pus cells	Negative
Mortality	Nil

3.2. Quantitative data on the body weight of rats treated with SBSMSC in Acute toxicity study

No significant change was observed in body weight of female rats treated with SBSMSC at the dose of 5000mg/ kg. The results were tabulated in Table 2.

Table 2: Body weight of rats in Acute toxicity study

Dose	Body weight in gms	
	Initial Body Weight (Before Treatment)	Final Body Weight (After Treatment)
SBSMSC 5000 mg/kg	183.2 ± 4.916	185.3 ± 4.761

Values are mean ± S.D (n = 6 per group).

3.3. Fecal Pellet consistency analysis of rats treated with SBSMSC in acute and sub-Acute toxicity study

Rats of control and treatment group were allowed to explore to open field on clean and sterile Stainless steel tray. The collected pellets were analyzed for consistency, color, Shape, Presence of blood cells etc. The results were tabulated in Table 3.

Table 3: Fecal Pellet consistency analysis of rats in acute and sub-Acute toxicity study

Acute Toxicity Study	
Analysis	**SBSMSC**
Consistency	Soft
Shape	Round Headed
Colour	Dark Green
Mucous Shedding	Absent
Blood Cells	Absent
Signs of Infection	None Observed

Sub-Acute Toxicity Study			
Analysis	**Control**	**Low Dose**	**High Dose**
Consistency	Rigid	Soft	Soft
Shape	Oblong	Round Headed	Round Headed
Colour	Greenish	Dark Greenish	Dark Greenish
Mucous Shedding	Absence	Absence	Absence
Blood Cells	Absent	Absent	Absent
Signs of Infection	None Observed	None Observed	None Observed

3.4. Assessment of clinical signs in rats treated with SBSMSC on Sub-Acute toxicity study

The dose of SBSMSC used for sub-acute toxicity study is 500 and 1000 mg/kg. No mortality observed at this dose level, further no significant change with respect to clinical signs on sub-acute toxicity observed for the period of 28 days. The results were tabulated in Table 4.

Table 4: Clinical signs of rats in Sub-Acute toxicity study

Clinical Signs Parameters for the duration of 28 days	Control	SBSMSC 500 mg/kg	SBSMSC 1000 mg/kg
Lacrimation	Absence	Absence	Absence
Salivation	Absence	Absence	Absence
Animal appearance	Normal	Normal	Normal
Tonic Movement	Absence	Absence	Absence
Clonic Movement	Absence	Absence	Absence
Laxative action	Absence	Absence	Absence
Touch Response	Normal	Normal	Normal
Response to Sound	Normal Response	Normal Response	Normal Response
Response to Light	Normal Response	Normal Response	Normal Response
Mobility	Normal Response	Normal Response	Normal Response
Respiratory Distress	Nil	Nil	Nil
Skin Color	Normal	Normal	Normal
Stereotype behavior	Absence	Absence	Absence
Piloerection	Absence	Absence	Absence
Limb Paralysis	Absence	Absence	Absence
Posture	Normal	Normal	Normal
Open field behavior	Normal	Normal	Normal
Giat Balancing	Normal	Normal	Normal
Freezing Behaviour	Absent	Absent	Absent
Sings of Stress and Anxiety	None Observed	None Observed	None Observed
Muscular coordination	Normal	Normal	Normal
Muscle grip	Normal	Normal	Normal
Sedation	Absence	Absence	Absence
Social Behavior	Normal	Normal	Normal
Urine Analysis	No Abnormality	No Abnormality	No Abnormality
Urine Colour	Yellowish	Yellowish	Yellowish
Urine pH	7	7	7
Urine -Glucose	Absence	Absence	Absence
Urine -Ketones	Absence	Absence	Absence
Urine- Bilirubin	Absence	Absence	Absence
Urine-Blood Cells	Negative	Negative	Negative
Urine - Pus cells	Negative	Negative	Negative
Mortality	Nil	Nil	Nil

3.5. Effect of SBSMSC on Body weight of Rats in Sub-acute toxicity study

No significant change was observed in body weight of both male and female rats treated with SBSMSC at low and high dose of 500 and 1000 mg/ kg b.w.The results were tabulated in Table 5.

Table 5: Body weight of rats in Sub-Acute toxicity study

Dose	Body weight in gms	
	Initial Body Weight (Before Treatment)	Final Body Weight (After Treatment)
Control	184.5 ± 4.37	211.5 ± 42.02
SBSMSC 500 mg/kg	188.7 ± 5.354	199.5 ± 3.937
SBSMSC 1000 mg/kg	184.3 ± 4.926	190.7 ± 4.32

Values are mean ± S.D (n = 6 per group of which 3 males and 3 females). Control and treatment groups were compared statistically using one way ANOVA followed by Dunnett's test.

3.6. Quantitative data on the food and water intake of rats treated with SBSMSC for 28 days in Sub-acute toxicity study

No statistically significant differences were recorded in food and water intake observation of rats treated with SBSMSC at low and high dose of 500 and 1000 mg/ kg b.w. The results were tabulated in Table 6.

Table 6: Food and water intake of rats in Sub-acute toxicity study

Dose	Average Food and Water Intake	
	Food Intake in gms	Water intake in ml
Control	14.83 ± 1.722	23.67 ± 2.066
SBSMSC 500 mg/kg	15.67 ± 1.751	24.5 ± 3.45
SBSMSC 1000 mg/kg	16.17 ± 2.041	23.67 ± 3.67

Values are mean ± S.D (n = 6 per group of which 3 males and 3 females). Control and treatment groups were compared statistically using one way ANOVA followed by Dunnett's test.

3.7.Effect of SBSMSC on Hematological parameters of rats in Sub-acute oral toxicity study

No statistically significant differences were recorded in hematological parameters of rats treated with SBSMSC at low and high dose of 500 and 1000 mg/ kg b.w. The results were tabulated in Table 7

Table 7: Hematological parameters of rats in Sub-acute oral toxicity study

Group	RBC ($\times 10^6$ µl)	WBC ($\times 10^3$ µl)	PLT ($\times 10^3$ µl)	HGB (g/dl)	MCH (pg)	MCV (fl)
Control	6.517 ± 0.7468	10.37 ± 1.479	418.3 ± 84.88	10.73 ± 4.054	19.13 ± 1.655	63.63 ± 4.752
SBSMSC 500 mg/kg	6.217 ± 1.27	8.583 ± 2.217	565.7 ± 129	11.73 ± 2.146	19.18 ± 2.351	61.33 ± 6.759
SBSMSC 1000 mg/kg	7.2 ± 1.649	8.683 ± 1.572	564.2 ± 114.8	11.58 ± 3.364	19.43 ± 1.776	56.12 ± 6.896

Values are mean ± S.D (n = 6 per group of which 3 males and 3 females). Control and treatment groups were compared statistically using one-way ANOVA followed by Dunnett's test.

3.8.Effect of SBSMSC on Hematological parameters of rats in Sub-acute oral toxicity study

No statistically significant differences were recorded in hematological parameters of rats treated with SBSMSC at low and high dose of 500 and 1000 mg/ kg b.w. The results were tabulated in Table 8.

Table 8: Hematological parameters of rats in Sub-acute oral toxicity study

Group	Neutrophils 10^3 /mm ^{3}	Eosinophils (%)	Basophils (%)	Lymph (%)	Mon (%)
Control	2.15 ± 0.6979	1.55 ± 0.251	0 ± 0	80.2 ± 8.415	2.25 ± 0.8313
SBSMSC 500 mg/kg	2.35 ± 0.9094	1.283 ± 0.2639	0.1667 ± 0.4082	81.07 ± 7.436	2.817 ± 1.388
SBSMSC 1000 mg/kg	1.933 ± 0.9522	1.6 ± 0.2	0.1667 ± 0.4082	83.53 ± 8.834	3.083 ± 1.141

Values are mean ± S.D (n = 6 per group of which 3 males and 3 females). Control and treatment groups were compared statistically using one way ANOVA followed by Dunnett's test.

3.9.Effect of SBSMSC on Serum Bio-chemistry profile of rats in sub-acute toxicity study

No statistically significant differences were recorded in serum biochemistry parameters of rats treated with SBSMSC at low and high dose of 500 and 1000 mg/ kg b.w. The results were tabulated in Table 9.

Table 9:Serum Bio-chemistry profile of rats in Sub-acute oral toxicity study

Group	BUN (mg/dl)	Serum Creatinine (mg/dl)	Total Bilirubin (mg/dl)	SGOT (IU/L)	SGPT (IU/L)
Control	16.5 ± 1.871	0.75 ± 0.1761	0.2333 ± 0.08165	102 ± 26.15	29.33 ± 11.2
SBSMSC 500 mg/kg	13.33 ± 2.066	0.6833 ± 0.1722	0.2667 ± 0.05164	120.2 ± 24.94	39.5 ± 11.64
SBSMSC 1000 mg/kg	16 ± 3.162	0.6833 ± 0.1472	0.3833 ± 0.1169	112.2 ± 28.02	24.5 ± 10.99

Values are mean ± S.D (n = 6 per group of which 3 males and 3 females). Control and treatment groups were compared statistically using one way ANOVA followed by Dunnett's test.

3.10.Effect of SBSMSC on Serum Bio-chemistry profile of rats in sub-acute toxicity study

No statistically significant differences were recorded in serum biochemistry parameters of rats treated with SBSMSC at low and high dose of 500 and 1000 mg/ kg b.w. The results were tabulated in Table 10.

Table 10: Serum Bio-chemistry profile of rats in Sub-acute oral toxicity study

Group	Total cholesterol (mg/dl)	HDL (mg/dl)	LDL (mg/dl)	VLDL (mg/dl)	TG (mg/dl)
Control	138.1 ± 7.627	59.83 ± 3.251	63.17 ± 6.242	15.08 ± 1.388	28.17 ± 4.262
SBSMSC 500 mg/kg	133.2 ± 12.35	54.67 ± 6.408	64.33 ± 11.79	14.2 ± 4.255	32.17 ± 9.326
SBSMSC 1000 mg/kg	138.3 ± 12.88	62.33 ± 7.891	62 ± 8.649	13.95 ± 2.816	32.17 ± 1.472

Values are mean ± S.D (n = 6 per group of which 3 males and 3 females). Control and treatment groups were compared statistically using one-way ANOVA followed by Dunnett's test.

3.11. Quantitative data on absolute Organ weight of male rats belongs to control and drug treated group in sub-acute toxicity study

No statistically significant differences were recorded in organ weight of male rats treated with SBSMSC at low and high dose of 500 and 1000 mg/ kg b.w. The results were tabulated in Table 11.

Table 11: Quantitative data on absolute Organ weight of male rats in sub-acute toxicity study

Group	Brain	Heart	Lung	Stomach	Liver	Spleen	Kidney	Testes
Control - Male	1.425 ± 0.1886	0.762 ± 0.1525	1.7 ± 0.7264	1.379 ± 0.5352	6.824 ± 1.46	0.69 ± 0.4311	1.586 ± 0.2905	1.9 ± 0.5
SBSMSC 500 mg/kg - Male	1.487 ± 0.4366	0.7987 ± 0.2439	1.037 ± 0.2412	1.495 ± 0.4307	3.83 ± 1.497	0.4533 ± 0.1793	1.181 ± 0.3651	2.82 ± 0.5212
SBSMSC 1000 mg/kg - Male	1.643 ± 0.02082	0.53 ± 0.04359	1.33 ± 0.1153	1.377 ± 0.1097	5.137 ± 0.4416	0.5367 ± 0.1007	1.023 ± 0.106	2.3 ± 0.4583

Values are mean ± S.D (n = 3 per group). Control and treatment groups were compared statistically

3.12. Quantitative data on absolute Organ weight of female rats belongs to control and drug treated group in sub-acute toxicity study

No statistically significant differences were recorded in organ weight of female rats treated with SBSMSC at low and high dose of 500 and 1000 mg/ kg b.w. The results were tabulated in Table 12.

Table 12: Quantitative data on absolute Organ weight of female rats in sub-acute toxicity study

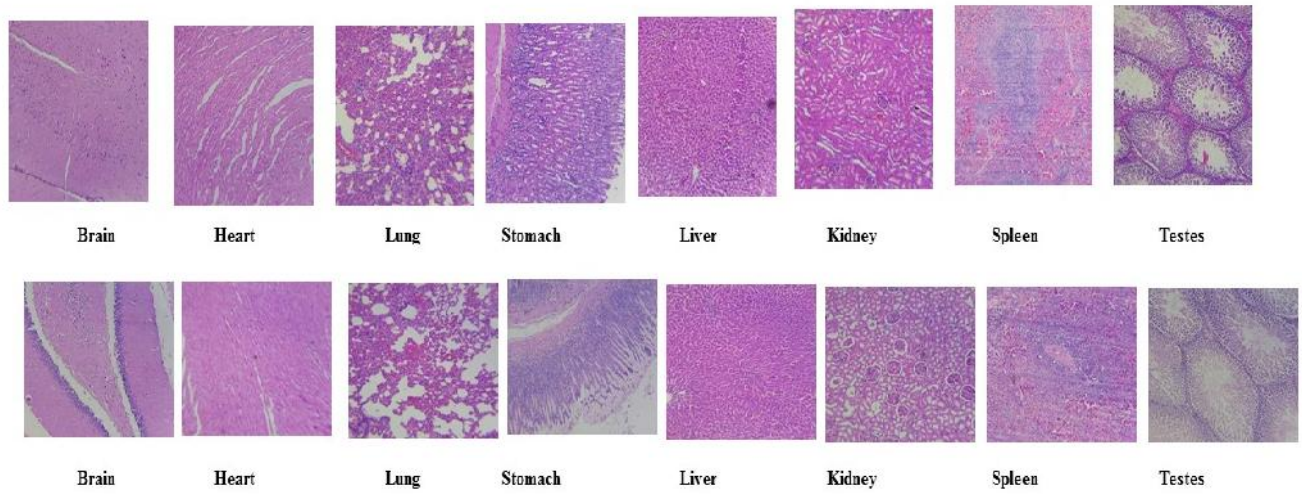
Group	Brain	Heart	Lung	Stomach	Liver	Spleen	Kidney	Uterus	Ovaries
Control -Female	1.75 ± 0.07835	0.9737 ± 0.09408	1.994 ± 0.4402	1.787 ± 0.09815	5.126 ± 0.6717	0.956 ± 0.1266	1.335 ± 0.08231	0.7957 ± 0.1555	0.4473 ± 0.04244
SBSMSC 500 mg/kg - Female	1.717 ± 0.3853	0.6533 ± 0.2723	1.633 ± 0.7223	1.463 ± 0.2957	5.15 ± 0.7402	0.5233 ± 0.1856	1.12 ± 0.3351	0.62 ± 0.02	0.33 ± 0.1552
SBSMSC 1000 mg/kg - Female	1.52 ± 0.2458	0.6067 ± 0.05132	1.097 ± 0.1779	1.59 ± 0.14	4.243 ± 0.2974	0.43 ± 0.1229	0.8733 ± 0.2031	0.8667 ± 0.07572	0.2733 ± 0.07506

Values are mean ± S.D (n = 3 per group). Control and treatment groups were compared statistically

3.13. Effect of SBSMSC on Histopathological changes of Male rat in Sub-acute oral toxicity study

Microscopic observation of vital organs belongs to male rats presenting the following architecture as shown in figure 1.

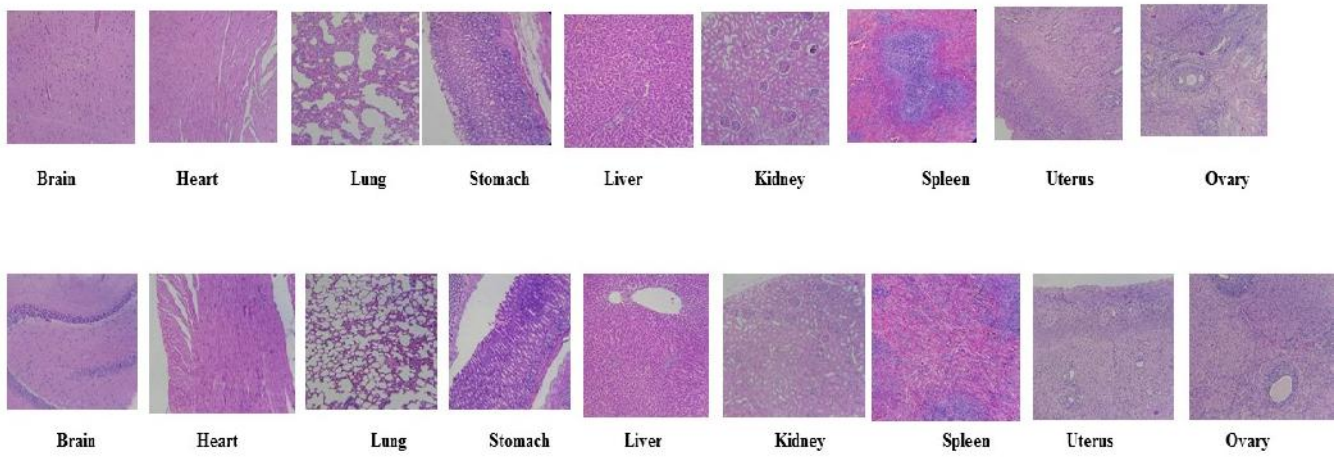
Figure 1: Histopathology of Male belongs to control and high dose treated group



3.14. Effect of SBSMSC on Histopathological changes of Female rat in Sub-acute oral toxicity study

Microscopic observation of vital organs belongs to female rats presenting the following architecture as shown in figure 2.

Figure 2: Histopathology of Female belongs to control and high dose treated group



4. Discussion

Various government agencies have continued to provide information on herbs including use patterns, toxicity information, clinical trial data, and review of reported side effects from herbal medicine use. Studies have linked several effects of medicinal products to an antioxidant system that help quench free radicals of different forms which are constantly generated for the specific metabolic requirement in the body. Reports from animal studies in respect to economic importance, toxicological effects and herb-drug interactions for commonly used herbal medicines [17,18]

The development of regulatory toxicology during the twentieth century up through the present has continued to shadow the ability to detect both chemicals and effects. That is, as it has become possible to detect toxicant at lower and lower levels as well as smaller biochemical and physiological changes, regulatory attention has turned to what appear to be new problems. In acute toxicity study, there was no mortality up to a maximum dose of 5000 mg/kg body weight of SBSMSC after per oral administration. The changes in bodyweight and other Clinical signs like skin color change, fecal consistency, gait analysis, urine analysis, sensory responses, animal behavior abnormalities, neuro muscular coordination have been used as an indicator of adverse effect. Since no remarkable changes were observed in animal behavior, body weight and organ weight at dose in treated rats as compared to control group, it can be inferred that siddha formulation SBSMSC is nontoxic at the administered dose of 5000mg/kg.

Hepatic and renal function analysis is a necessary thing within the toxicity analysis of any herbal preparation as they are important for the functioning of normal physiology [19]. In sub-acute toxicity study treatment with SBSMSC at 500 and 1000 mg/kg reveals no significant change in the any of the serological analysis such asfor High Density Lipoprotein (HDL), Low density Lipoprotein (LDL), Very low density Lipoprotein (VLDL), Triglycerides (TGL), Total Cholesterol, Blood urea nitrogen (BUN), Creatinine, Albumin, Total Protein, Glucose, Uric acid, Aspartate Transaminase (AST), Alanine amino Transaminase (ALT) and Alkaline Phosphatase (ALP) in both male and female rats.

The histological examination of all vital organs of both control ad treatment group rats revealed that none of the organs of treated rats revealed alteration and there were no abnormalities in the cell structure of these vital organs. The granule cells of brain hippocampi appear normal, normal histology of heart myocardial fibres with no evident of necrotic fibres evident, similarly normal alveoli with equidistant arrangement and prominent histology in lung, Gastric glands, gastric glands including secretary sheath appears normal in stomach.

Liver sinusoid appears widen with occasional bi nucleated hepatocytes were observed, histology of Kidney section shown mildly shrunken glomeruli (G) with widen capsular Bowman's space. Morphology of capsule, nodes, red and white pulp appears normal in spleen. Primary spermatocytes with large centered nucleus and dense chromatin were observed in testes.Uterus of female rat’s projects regular histology of uterine epithelium and endometrial glands and section of ovary showing well follicular development, Pre-ovulatory follicle surrounded by granulosa cells with normal zona pellucida and theca interna and externa observed in ovary.

5. Conclusion

Folklore use of herbals was very common in rural areas, the use of herbal preparations for the treatment of various ailments is still very common. The results of the present study strongly suggest that the siddha formulation Sarabendira siddha maruthuva sudar chooranam was absolutely safe and was well tolerated at the tested oral doses in both acute and sub- acute toxicity studies in experimental rats. From the observation it was evident that long-term usage of this formulation may be considerably safe and shall be utilized for therapeutic benefits in humans with proper preclinical validation.

Acknowledgments

I wish to acknowledge my thanks to The Tamil Nadu Dr. M.G.R. Medical University, Chennai, Tamil Nadu, India and The Noble research solutions, Chennai, Tamil Nadu, India for their support.

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How to cite this article:
K.Dhivyalakshmi, S. Arul Jothi, N. Anbu, D.Sivaraman. (2019). Preclinical Safety Evaluation of Sarabendira Siddha Maruthuva Sudar Chooranam by Acute and Subacute repeated oral toxicity Studies in Rodents. Int. J. Curr. Res. Biol. Med. 4(10): 1-12.
DOI: http://dx.doi.org/10.22192/ijcrbm.2019.04.10.001

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