Acute and Sub-chronic Toxicity (90-Day) Study of Swamala (SWA)® in Wistar Rats.

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ABSTRACT

Background: Swamala (SWA)® is an Ayurvedic proprietary product used in the treatment of general debility and in immune-compromised conditions. Despite its usefulness, there is no published data on toxicity profile of SWA®. Objective: The main objective of the present study was to evaluate safety of SWA® in an acute and 900 day repeated dose toxicity study in Wistar rats. Methods: SWA® at the doses of 0, 3, 6, and 15 g/kg was administered for 90 consecutive days. Body weights and feed consumption were recorded and analyzed. At termination of the study rats were sacrificed and observed for gross pathological changes. All organ parts were collected, weighed and preserved for histopathological examination and blood was collected from retro-orbital sinus for clinical biochemical analysis. Results: After 90 days of oral administration SWA® did not show any gross toxicological signs and histopathology also when compared with normal. All animals in Group IV showed significant increase in body weight as compared to that of control group animals. No mortality was observed throughout the period. Conclusion: Finally, it was concluded that SWA® having no toxico-pathological effects at a dose of 15 g/Kg which is equivalent to five times the therapeutic dose administered orally for 90 days.

Introduction

Ayurveda is the science of life which mainly deals with maintenance of health or diseases of humanity by holistic approach. Ayurvedic doctrine of treatment is mainly rely on Panchamahabhuta (earth, water, air, fire, and space), saptadhatu (seven vital functionaries of physiology), Tridoshas (three fundamental humors), and etc. In Ayurveda, we may categorize all Ayurvedic preparations into two groups i.e. Kashthaoushadhis (herbal preparations) and Rasashaushadhis (herbo – bio – metallic - mineral preparations). Rasashastra may be defined as a branch of Ayurveda which deals with various pharmaceutical processes of Shodhana (purification), Marana (incineration/calcification), Jarana (polling), and Murchana (by which substances transformed for therapeutic application) and other details of different processes.

The term “Life style Disorders” is becoming very popular in 21st century. Because, there is revolutionized industrialization along with modified life style conditions i.e. lack of exercise, sedentary life style, and dietary changes etc. All of these events lead to changes in health status of human beings i.e. oxidation system, general debility, immunity, and life style disorders. In light of this, substances/ingredients having the antioxidant property are mainly being used for treatment various diseases developed due to changes in equilibrium of antioxidant system.

Besides, there is a tremendous development of modern medicine; there are some areas in which modern medicine have failed to prove its effectiveness like, side effects, cost of drugs, relapse, and lack of curative treatment. So, it draws our attention towards alternative system of medicine. In India, about 80 % of population depends on traditional medicine, out of which, nearly 70-75 % depend on the Ayurvedic medicine. Moreover, different types of metals like Mercury (Hg), Arsenic (As), Iron (Fe), Copper (Cu), and Gold (Au) are used in preparation of different Ayurvedic preparations in the form of Bhasmas, ashes and/or organo-metallic compounds, are claimed to produce quick action, lesser dose, tastelessness, prolonged shelf-life, and better palatability. Hence, demonstrating the safety of metal based Ayurvedic preparations is of paramount importance.

Being a time tested healthcare system “Ayurveda” is now actual facet of evidence as being complementary system of medicine. However, there is a lack of information on the safety and efficacy profiles of Ayurvedic preparations. In spite of this, there is precipitously increasing number of reports of toxic effects of Ayurvedic preparations, after using long term use and increased outcry about safety of this Bhasmas. In this condition, there is a need of well planned toxicity study following the regulatory requirement. Ayurvedic preparations are mostly herbo-mineral
products, poly or mono herbal formulations. In recent years, there is increased utilization of herbal preparations under dietary supplements, under the Dietary Supplement Health and Education Act (DSHEA). Herbal preparations are more or less toxic than prescription medicines. So there is a need of toxicity studies to market the product using highest dose levels to determine end point organ toxicity.

Swamala (SWA) is an Ayurvedic semisolid preparation of Shree Dhootapapeshwar Limited (SDL), Mumbai. Swamala is mainly prescribed in situations of general debility and in immune-compromised conditions due to the presence of Chyawanprash as the chief ingredient. Various pharmacological activities are attributed for the ingredients of swamala, they are Chyawanprash for the immunomodulatory, hepatoprotective, antioxidant, and genoprotective activity, Suvarna bhasma for immunomodulatory and antiarthritic potential, Raupya bhasma for analgesic activity, Abhraka bhasma for hepatoprotective activity.

**Composition of Swamala (SWA)**

Each 10 gram contains:

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chyawanprash (Ashtavarga)</td>
<td>9.959 g</td>
</tr>
<tr>
<td>Suvarna bhasma (Gold)</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Raupya bhasma (Silver)</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Abhraka bhasma (Mica)</td>
<td>5.0 mg</td>
</tr>
<tr>
<td>Kantaloha bhasma (Iron)</td>
<td>10.0 mg</td>
</tr>
<tr>
<td>Makardhwaj (Poornachandrodaya)</td>
<td>14.0 mg</td>
</tr>
</tbody>
</table>

We, therefore, undertook this study to evaluate the repeated dose (90 Days) oral toxicity of swamala in Wistar rats to identify the toxicological profile and targets of organ toxicity.

**Materials and Methods**

**Acute Toxicity**

Acute oral toxicity of the polyherbal formulation was carried out as per the guidelines set by the Organization for Economic Co-operation and Development (OECD), revised draft guidelines 423. Overnight fasted rats were orally fed with the swamala in increasing dose levels of 5, 50, 300, and 2000 mg/kg b.wt., respectively. The test drug was suspended in 2% carboxy methyl cellulose (CMC) solution and given in graded doses up to maximum level. Animals were observed for toxicological signs for 24 hrs and subsequently for 14 days.

**Sub chronic toxicity**

**Animals**

80 Wistar rats of either sex weighing between 100-120g were procured from the Hoffkine’s Biopharmaceutical Pvt. Ltd., Parel, Mumbai. Rats were allowed acclimatization period of 7 days to laboratory conditions prior to the initiation of the study. Also, all the animals were subjected to veterinary examination. Rats were assigned to the cages, sex wise, three per cage and the individual animals were fur marked. The females were nulliparous and non-pregnant. Paddy husk was used as a bedding material in cages housing the animals and was changed every day. A 12-hour light/dark cycle was provided throughout the study period. Animals had free access to food and water. Environmental conditions were maintained at an ambient temperature of 23°C ± 2°C and a relative humidity of 40 - 70%. The study was approved by the Institutional Animal Ethics Committee (SDARF/CT/2010-11/01). The dose for the study was calculated from the basis of human therapeutic dose (HTD) 30 g/day. swamala was obtained from the Shree Dhootapapeshwar Limited (SDL), Mumbai.

**Experimental Design**

As per OECD guidelines 408.

- **Group I:** Control (Vehicle alone)
- **Group II:** Low dose (3 g/kg)
- **Group III:** Moderate dose (6 g/kg)
- **Group IV:** High dose (15 g/kg)

The test substance swamala was suspended in 2% CMC in distilled water and was administrated to the test animals continuously for 90 days at low dose, moderate dose and high dose in the dose volume of 1 ml/100 g b.wt through oral gavage intubation. The suspensions of the test substance were prepared freshly, every day for all the 90 days. The control animals were administered vehicle alone in the same volume in a similar manner.

All rats were observed daily for the clinical signs and mortality. Body weights and feed consumption were recorded weekly. After completion of 90 days administration the blood was withdrawn from the retro-orbital sinus for the biochemical and hematological parameters and rats were sacrificed using CO2 asphyxiation. All organs were properly examined for the gross pathological changes, weighed and collected in 10 % formalin solution and testes were collected in modified Bouin’s solution. Organs from the high dose and control group were processed as per RTA guidelines.

For hematological examination, the following parameters were evaluated i.e. Hemoglobin (Hb), Reticulocytes, Red Blood Corpuscles (RBC), Platelets, White Blood Corpuscles (WBC), Basophils (B), Neutrophils (N), Lymphocytes (L), Eosinophils (E) (%), Monocytes, Packed Cell Volume (PCV). Biochemical investigations like Blood Urea Nitrogen (BUN), Urea, Serum Glutamic Pyruvic Transaminase (SGPT), Serum Glutamic Oxaloacetic Transaminase (SGOT), Alkaline Phosphatase (ALP), Albumin, Total Protein (g/dl), Creatinine (CRE) (mg/dl), Sodium (Na+) (mEq/l), Potassium (K+) (mEq/l), Chloride (Cl-) (mEq/l), Cholesterol (CHO) (mg/dl), Calcium (Ca++) (mg/dl), Phosphorus (P++) (mg/dl), Triglyceride (mg/dl), Globulin (g/dl), Glucose (mg/dl), Total
Bilirubin (Total Bili.) (mg/dl) were estimated.

**Clinical observations**

Detailed clinical examination included identification of clinical signs related to: general appearance, body position and posture, autonomic nervous system function, motor coordination, reaction to being handled and to environmental stimulation, nervous system (e.g., tremor, convulsion, muscular contractions), changes in exploratory behavior, abnormal behavior (e.g., autophagia, abnormal vocalization, backward motion) and aggression.

**Statistical Analysis**

All data are presented as mean ± SD. The values obtained in the four treated groups were compared with those recorded in the control group of animals for statistical significance of differences, if any, using analysis of variance (ANOVA).

**Results**

**Acute Toxicity**

There is no abnormality in rats up to 4 hours followed by 14 days and no mortality and no toxicological symptoms were observed.

**Sub Chronic Toxicity**

**Effect on Body Weight and Feed Consumption**

Swamala was tested for 90 days oral chronic toxicity study in Wistar rats after reviewing and summarizing the body weights of all male and female rats. There was no significant difference in bodyweight and feed consumption in any animal of any of the treatment groups, except Group IV, when compared with that of the control group. All animals in Group IV showed significant increase in body weight as compared to that of control group animals (Unpublished data).

**Clinical signs and Mortality**

No mortality was observed throughout the study. Faecal consistency and secretions were normal.

**Hematological and Serum Biochemical Parameters**

Hematological and serum biochemistry parameters showed no significant differences between the control group and all the treated groups studied (Table 1, 2, and 3).

<table>
<thead>
<tr>
<th>Gr. No.</th>
<th>Dose (g/kg)</th>
<th>Hb (g/dl)</th>
<th>Reticulocytes (%)</th>
<th>Total RBC (x10^6)</th>
<th>Platelets (x10^5/cmm)</th>
<th>Total WBC (x10^3/cmm)</th>
<th>Hematocrit (%)</th>
<th>Differential Count (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Control</td>
<td>13.44</td>
<td>2.77</td>
<td>6.57</td>
<td>5.62</td>
<td>15.65</td>
<td>42.58</td>
<td>0.00 25.80 72.50 0.70 1.00</td>
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<tr>
<td>II</td>
<td>3</td>
<td>13.48</td>
<td>2.94</td>
<td>7.12</td>
<td>5.4</td>
<td>14.54</td>
<td>42.28</td>
<td>0.10 26.00 72.00 1.10 0.90</td>
</tr>
<tr>
<td>III</td>
<td>6</td>
<td>13.45</td>
<td>2.76</td>
<td>6.49</td>
<td>6.02</td>
<td>14.43</td>
<td>41.20</td>
<td>0.00 30.20 67.70 0.80 1.30</td>
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<tr>
<td>IV</td>
<td>15</td>
<td>13.93</td>
<td>2.86</td>
<td>6.66</td>
<td>6.00</td>
<td>15.23</td>
<td>41.62</td>
<td>0.00 26.90 71.30 0.90 0.90</td>
</tr>
</tbody>
</table>

(p< 0.05 as compared to control)
Hb: Hemoglobin
RBC: Red blood Corpuscles
WBC: White Blood Corpuscles
B: Basophils
N: Neutrophils
L: Lymphocytes
E: Eosinophils
M: Monocytes

**Organ Weights**

No significant differences were seen in the organ weight data of animals from different dose groups when compared with those of respective control group (Table 4 and 5).

None of the animals in all treated groups showed any macroscopic or gross pathological changes on necropsy when compared to the control group.

**Histopathological Analysis**

None of the animals in the high dose treatment group (Group IV) did not show any drug related histopathological changes in any of the organs studied, when compared with those from the control group animals (Figure 1-9).

**Discussion**

_Ayurveda_ is one of the oldest systems of medicine practicing over 5000 years in India. However, the major drawback in this system of medicine is lack of standardization, safety and efficacy and there is a lack of supporting data regarding its safety and efficacy in clinical trials. Heavy metals toxicity is a major concern over the _Ayurvedic_ formulations due to
presence of Lead, Arsenic, and/or Mercury, etc and context of Ayurveda describes various physiochemical processes like sublimation, heating, etc. to detoxify toxic metals to therapeutic preparations. Now-a-days, there is increased number of herbo-mineral preparations to treat various ailments like anemia, cancer, diabetes, and skin diseases, etc. as per WHO list of traditional medicines in Asia. There are number of reported uses of herbo-mineral preparations i.e. Prakash et al. reported Prak-20, that is helpful in abrogating carbon tetra chloride (CCL4) induced hepatotoxicity, Azith Vaze reported beneficial effect of Addyza in oligospermia in comparison with Ubiquinone (Co-enzyme Q10).

Table 2. Group mean of Biochemical investigations (mean ± SD) (n = 20)

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Dose (g/kg)</th>
<th>SGOT (IU/L)</th>
<th>SGPT (IU/L)</th>
<th>ALP (IU/L)</th>
<th>Total protein (g/dl)</th>
<th>Albu min (g/dl)</th>
<th>UREA (mg/dl)</th>
<th>Ca++ (mg/dl)</th>
<th>P++ (mg/dl)</th>
<th>Tri- glycerides (mg/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Control</td>
<td>179.00</td>
<td>59.00</td>
<td>404.40</td>
<td>6.31</td>
<td>2.84</td>
<td>43.19</td>
<td>13.13</td>
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<td>21.63</td>
<td>9.24</td>
<td>82.41</td>
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<td>0.80</td>
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<td></td>
<td>185.50</td>
<td>61.70</td>
<td>379.80</td>
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<td>41.88</td>
<td>13.43</td>
<td>6.63</td>
<td>72.20</td>
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<tr>
<td>II</td>
<td>3</td>
<td>15.29</td>
<td>8.15</td>
<td>84.34</td>
<td>0.67</td>
<td>0.56</td>
<td>5.29</td>
<td>1.18</td>
<td>0.93</td>
<td>6.96</td>
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<tr>
<td>III</td>
<td>6</td>
<td>181.30</td>
<td>61.90</td>
<td>366.40</td>
<td>6.74</td>
<td>3.07</td>
<td>40.82</td>
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<td>14.71</td>
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<td>47.26</td>
<td>0.74</td>
<td>0.97</td>
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<td>1.33</td>
<td>0.81</td>
<td>8.07</td>
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<td>IV</td>
<td>15</td>
<td>181.80</td>
<td>56.36</td>
<td>404.90</td>
<td>6.57</td>
<td>2.95</td>
<td>41.23</td>
<td>13.27</td>
<td>7.15</td>
<td>70.20</td>
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<tr>
<td></td>
<td>13.70</td>
<td>7.59</td>
<td>104.44</td>
<td>0.86</td>
<td>0.66</td>
<td>4.71</td>
<td>1.68</td>
<td>0.90</td>
<td>7.45</td>
<td></td>
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</tbody>
</table>

(ρ< 0.05 as compared to control)
SGOT: Serum glutamic oxaloacetic transaminase
SGPT: Serum glutamic pyruvic transaminase
ALP: Alkaline Phosphatase
Ca++: Calcium
P++: phosphorous
TRG: Triglycerides

Table 3. Group mean of Biochemical investigations (mean ± SD) (n = 20)

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Dose (g/kg)</th>
<th>BUN (mg/dl)</th>
<th>CRE. (mg/dl)</th>
<th>Na⁺ (mEq/l)</th>
<th>K⁺ (mEq/l)</th>
<th>Cl⁻ (mEq/l)</th>
<th>CHO. (mg/dl)</th>
<th>Globulin (g/dl)</th>
<th>Glucose (mg/dl)</th>
<th>Total Bili. (g/dl)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Control</td>
<td>26.29</td>
<td>0.56</td>
<td>141.00</td>
<td>3.90</td>
<td>102.80</td>
<td>72.60</td>
<td>2.48</td>
<td>74.20</td>
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<td></td>
<td>2.69</td>
<td>0.11</td>
<td>5.83</td>
<td>0.95</td>
<td>2.82</td>
<td>13.02</td>
<td>0.34</td>
<td>17.97</td>
<td>0.11</td>
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<tr>
<td></td>
<td>23.72</td>
<td>0.48</td>
<td>142.30</td>
<td>4.50</td>
<td>104.60</td>
<td>67.60</td>
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<td>75.20</td>
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<td>3.19</td>
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<tr>
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<td>25.53</td>
<td>0.60</td>
<td>144.20</td>
<td>4.39</td>
<td>103.50</td>
<td>73.00</td>
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<td>11.09</td>
<td>0.15</td>
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<tr>
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<td>6</td>
<td>25.20</td>
<td>0.56</td>
<td>142.80</td>
<td>4.37</td>
<td>102.60</td>
<td>74.40</td>
<td>2.73</td>
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<tr>
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<td>0.13</td>
<td>7.42</td>
<td>0.47</td>
<td>2.76</td>
<td>9.89</td>
<td>0.51</td>
<td>15.82</td>
<td>0.13</td>
<td></td>
</tr>
</tbody>
</table>

(ρ< 0.05 as compared to control)
BUN: Blood Urea Nitrogen
Na⁺: Sodium
K⁺: Potassium
Cl⁻: Chloride
Total Bili.: Total Bilirubin
CHO.: Cholesterol
CRE.: Creatinine

Heavy metals are toxic, but their oxides are purely safe and 
Bhasmas are naturally safe, if they are prepared as per scientific scripts, when these preparations are prescribed with different Ampanas (accompaniments), e.g., ginger, cumin water, and tulsi extract, etc. Two gold Ayurvedic preparations, i.e. Suvarna Bhasma (Gold) and unani Kashta Tila Kalan are claimed to possess general tonic, nerve tonic, Hepatoprotective, and antiaging properties. Tamra Bhasma (Copper), a metallic preparation is used for various ailments specifically free radicals mediated diseases and it also reduces lipid peroxidation (LPO), induces the activity of super oxide dismutase (SOD), reduced glutathione levels in rat liver homogenate in the biphasic manner. Although, there have increasing an increasing number of toxicity symptoms of published heavy metal
poisoning, after use of traditional medicines.

Hence, the present study was initiated to evaluate the sub chronic toxicity profile of swamala in Wistar rats. The test compound did not show any toxicological effect on weekly body weight, feed consumption, and clinical signs and symptoms throughout the study. Hematological and biochemical parameters were comparable with the control group. There are no significant differences in absolute and relative organ weights, and histopathology in all treated groups.

Hence, the multi-ingredient concept of Ayurvedic therapy delineates the counter balancing of negative or toxic effects of ingredients, i.e., herb or metals (*Bhasmas*). Several metallic preparations are used for various clinical conditions since 12th century, and these *Bhasmas* are safe after processing using *Shodhan*, *Maran*, and *Sublimation*, etc. Moreover, due to presence of Chyawanprash it is helpful in peptic ulcer, gastritis, intestinal cramping, hepatoprotective, strengthens liver, respiratory system, corrects the metabolism of fats and proteins, and cardiotonic. It is also having the anti-oxidant, anti-carcinogenic and anti-mutagenic activity, enhances libido and fertility in both sexes.

**Conclusion**

Oral administration of swamala at a 15 g/kg b.w which is equivalent to five times the therapeutic dose administered orally for 90 days did not show any toxicological signs. Body weight and estimated feed consumption were not affected, no hematological or biochemical alterations were noted. No mortality was observed and did not observe any gross lesions and histopathological changes in all treated groups. Therefore, the test substance swamala can be considered safe for human therapeutic use at the recommended therapeutic doses and regimen for long term use.

**Acknowledgements**

This work was supported by Shree Dhoogapapeshwar Limited (SDL), Mumbai. We thank Dr. D. P. Chaudhari, M. V. Sc. (Pathology) for the histopathological analysis.

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Dose (g/kg)</th>
<th>Body Wt. (g)</th>
<th>Kidneys (g)</th>
<th>Liver (g)</th>
<th>Adrenals (mg)</th>
<th>Testes (g)</th>
<th>Spleen (g)</th>
<th>Heart (mg)</th>
<th>Lungs (mg)</th>
<th>Brain (mg)</th>
<th>Epididymis (g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Control</td>
<td>305.48 2.51 13.89 55.88 3.42 1354.93 1055.93 1.23 2.49 1.63</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II 3</td>
<td>308.06 2.41 14.50 58.14 3.31 1454.43 1130.20 1.18 2.39 1.61</td>
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<td></td>
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<td>III 6</td>
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</table>

*(p< 0.05 as compared to control)*

<table>
<thead>
<tr>
<th>Group No.</th>
<th>Dose (g/kg)</th>
<th>Body Wt. (g)</th>
<th>Kidneys (g)</th>
<th>Liver (g)</th>
<th>Adrenals (mg)</th>
<th>Spleen (g)</th>
<th>Ovaries (mg)</th>
<th>Heart (mg)</th>
<th>Lungs (mg)</th>
<th>Brain (mg)</th>
<th>Uterus (g)</th>
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<tbody>
<tr>
<td>I Control</td>
<td>230.37 2.18 11.07 70.29 179.24 155.13 991.12 1.14 2.27 171.63</td>
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*(p< 0.05 as compared to control)*
Jonnalagadda et al.

Figure 1. Photomicrograph of Liver

A (control) B (treated one)

Figure 2. Photomicrograph of Heart

A (control) B (treated one)

Figure 3. Photomicrograph of Kidney

A (control) B (treated one)

Figure 4. Photomicrograph of Lung (control)

A (control) B (treated one)
Figure 5. Photomicrograph of cerebellum (control)

Figure 6. Photomicrograph of cerebrum (control)

Figure 7. Photomicrograph of testis

Figure 8. Photomicrograph of ovary
References


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