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# Evaluation of acute, sub-acute toxicity and cardiac activity of processed borax

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Borax is used in Ayurveda to treat various diseases like asthma, ulcer, and others, after removal of the water for crystallisation. It causes toxicity when accumulated in the body, leads to vomiting, fatigue, and renal failure. The present study was carried out to evaluate the acute and the sub-acute toxicity and cardiac activity of processed borax in rats. Acute toxicity of processed borax was observed at the doses of 112.5, 225.0, 450.0, 900.0, and 1800.0 mg/kg. Processed borax solution at 22.5 and 112.5 mg/kg/day dose was administered for 30 consecutive days in sub-acute toxicity study. Cardiac activity of processed borax was studied by giving a borax solution at 22.5 and 112.5 mg/kg/day dose for 30 days and taking ECG. In the acute toxicity test, the processed borax did not produce any deaths. The sub-acute treatment with the processed borax (22.5 and 112.5 mg/kg, n = 6/group) failed to induce serious alterations in almost all the parameters, except toxicity in the kidney at 112.5 mg/kg. No change in ECG was observed in cardiac activity study. The $LD_{50}$ of processed borax is above 1.8 mg/kg. It has no serious toxicity on sub-acute exposure and has no pathological intervention on the heart in rats.

**Keywords:** Ayurveda, Borax, Cardiac activity, ECG, $LD_{50}$, Sub-acute toxicity.

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## Introduction

Borax is one of the oldest known minerals used in therapeutic in Ayurvedic system of medicine. It is used for various therapeutic purposes both internally and externally after dehydration by heating. The processed borax is used internally to pacify diseases like bronchial asthma, cough, cardiac ailments, for treatment of poisoning and others; and externally it is used for the treatment of skin diseases, ulcer and others[1]. It is also used as an antidote for aconite poisoning in Ayurveda[2,3].

Borax has well-defined biological effects and may be of therapeutic benefit. The effect of boron in the form of borax was tested in an experimental animal model of fulminant hepatic failure. And the study reported that borax partly normalises the liver and offsets the deleterious effects observed in fulminant hepatic failure by modulating the oxidative stress parameters[4]. Borax acts as an adsorbent, and by using this activity, it is also tested for targeted drug delivery in the malignant tumour site. One study reported that two-component ultra-dispersed particles containing iron and carbon were tested as magnetic adsorbents of boron phenylalanine and borax. The quantities of absorbed borax proved sufficient for a high concentration of boron atoms at the tumour site[5]. Borax is used as an antidote in fluoride intoxication. It has some value as an antidote through the formation of a fluoborate. Boron administered during fluoride intoxication or after its interruption, reduces fluoremia and increases urinary fluoride excretion. Skeletal fluoride levels are directly related to those of claws[6].

Systemic exposure (e.g., ingestion) to borax has been associated with reversible toxic alopecia among other manifestations. Occupational topical exposure to borax in solutions may cause reversible alopecia. Serious nuclear and cytoplasmic lesions and numerous apoptotic lesions in the thymus caused by borax in Wister rats were observed in a recent study[7]. Borax generally displays low acute toxicity orally, dermally, and by inhalation. It is either not irritant on mild skin or eye irritants. Borax has the toxicity to humans, including reproductive and developmental toxicity, neurotoxicity, and nephrotoxicity. The degree of borax toxicity depends on the dose or concentration that the human received. The most

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sensitive endpoints of borax toxicity are developmental and reproductive toxicity[8]. But one of the studies claimed no effects on fertility in a population of workers exposed to borates or a population exposed to high environmental borate levels[9].

The aim of the present study was to assess whether the processed borax which is used in Ayurvedic practice as medicine produces any toxicity and cardiac activity in Charles Foster albino rats. For this toxicological evaluation, some protocols are indispensable, such as acute and subacute toxicity, including haematological, biochemical and histological analyses. The cardiac activity was assessed by taking and interpreting the electrocardiogram (ECG) of the rats.

## Materials and Methods

### Drug material

The raw borax was collected from the Pharmacy of Gujarat Ayurved University, Jamnagar, Gujarat, India. It was made into coarse powder (22 mesh size) form and heated at 450 $^{o}$C to remove the water for crystallisation; the yield was 54 %. The processed borax was made into fine powder (200 mesh size) form. The drug solution was prepared by dissolving the powder in distilled water and used for the study. Considering the adult human dose of processed borax to be 250 mg[10], the dose for the experimental study was calculated by extrapolating the human dose to animal dose based on the body surface area ratio as 22.5 mg/kg[11].

### Animals

Adult male and female Charles Foster strain albino rats, aged 2 months, weighing between 180 g to 250 g were used for experiments. They were obtained from the Animal House attached to the pharmacology laboratory of Gujarat Ayurved University, Jamnagar. They were housed in breeding cages at ambient temperature with a natural day and night cycles. The animals had free access to Amrut brand rat pellet feed supplied by Pranav Agro Industries and tap water. The experimental protocol was approved by the Institutional Animals Ethics Committee of Gujarat Ayurved University (IAEC-06-08/02).

### Acute toxicity study

Healthy rats of either sex fasted overnight but allowed access to water *ad libitum* were randomly divided into six groups (n = 3/group). The first group (control group) received water. Groups 2-6 were orally treated with a solution of processed borax at the doses of 112.5, 225.0, 450.0, 900.0, and 1800.0 mg/kg, respectively. Animals were observed for general behavioural and body weight changes, hazardous symptoms and mortality for 7 days after treatment. The lethal dose ($LD_{50}$) was estimated according to the method described by Litchfield and Wilcoxon[12].

### Sub-acute toxicity study

Eighteen rats were randomly divided into 3 group, each containing an equal number of male and female rats (n= 6/group). Animals of group 1 received water vehicle orally (control group); group 2 and 3 were orally treated with a borax solution at the doses of 22.5 and 112.5 mg/kg/day, respectively for 30 consecutive days. The body weight was recorded weekly, and their food and water intake were monitored daily. Animals were observed for signs of abnormalities during the treatment period. At the end of the treatment, animals were fasted overnight but allowed access to water *ad libitum*, body weights were recorded, and the animals were sacrificed by stunning. Blood was collected by puncturing the heart with or without anticoagulant (ethylenediamine tetraacetate). Blood with the anticoagulant was used immediately for the determination of haematological parameters, while blood without the anticoagulant was centrifuged at 4000 rpm for 10 min and the serum obtained was used to determine the biochemical parameters. The vital organs were dissected carefully; weights were recorded, and organs were preserved in 10 % formaldehyde solution for histopathology study.

### Cardiac activity study

The cardiac activity was evaluated by taking an electrocardiogram (ECG) after administration of test drugs. 18 rats of either sex were divided randomly into 3 groups, each containing 6 animals, 3 male and 3 female. The treatment schedule was as follows, group 1 comprised of the vehicle (tap water) treated control animals, and group 2 and 3 animals were treated with 22.5 mg/kg and 112.5 mg/kg, processed borax solution, respectively. The treatment schedule was continued for 30 days and ECG was taken after 1 h of drug administration on the 1$^{st}$, 15$^{th}$, and 30$^{th}$ day. The rats were anesthetised by using diethyl ether. ECG was recorded by using a portable electrocardiogram machine. Only the four standard leads were attached to the four extremities of the animals; the chest leads were not used. The paper

speed of the ECG machine was set to 50/sec. The parameters like heart rate, duration of QRS complex and R-R interval was counted from lead II of the ECG.

#### Statistical analysis

The results are expressed as mean±SE (standard error). The data was assessed by Student's t-test and one-way analysis of variance (ANOVA) followed by Dunnet's Multiple Comparison test. A probability level of less than 5 % ($p$ <0.05) was considered significant.

## Results

#### Acute toxicity study

The results indicated that treatment by processed borax solution through oral route at doses up to 1.8 g/kg did not produce any sign of toxicity or death in rats during 7 days of observation. Therefore, the $LD_{50}$ could not be estimated, and it is possibly more than 1.8 g/kg.

#### Sub-acute toxicity study

Changes in body weight of control and processed borax treated rats are presented in Table 1. Rats gained weight with time (as expected), with no significant difference in weight gain at the end of 30 day treatment between control and rats treated with 22.5 and 112.5 mg/kg dose of processed borax solution; weight gain in rats treated with the higher dose of the solution (112.5 mg/kg) appeared to be suppressed. The weights of the vital organs are depicted in Table 2. Weight of testis increased significantly, and weight of thymus decreased significantly in processed borax solution with a lower dose (22.5 mg/kg) treated rats (as compared to control rats). The weights of other organs were not changed even to a moderate level by the administration of both of the dose levels of the test drug.

Table 1—Effect of two dose levels of test drug by oral route on body weight in Charles Foster albino rats treated consecutively for 30 days

| Groups | Dose (mg/kg) | Body weight (g) | |
|---|---|---|---|
| | | Initial | Final |
| Control | -- | 211.67±08.12 | 227.67±07.97** |
| ST 1 | 22.5 | 220.33±07.33 | 247.67±13.10* |
| ST 5 | 112.5 | 223.33±06.92 | 231.33±07.02* |

The values are expressed as mean±SE (n = 6 animals/group). *, ** Statistically significant and highly significant difference, $p$ <0.05, $p$ <0.01, respectively by Student's t-test, as compared with initial values.

Table 2—Effect of two dose levels of test drug by oral route on ponderal parameters in Charles Foster albino rats treated consecutively for 30 days

| Organs | Weight | Groups (Dose mg/kg) | | |
|---|---|---|---|---|
| | | Control (--) | ST1 (22.5) | ST5 (112.5) |
| Liver | Absolute (g) | 6.84±0.64 | 8.12±0.56 | 6.41±0.29 |
| | Relative (g %) | 2.98±0.22 | 3.32±0.14 | 2.78±0.16 |
| Heart | Absolute (g) | 0.76 ± 0.04 | 0.77±0.03 | 0.74±0.02 |
| | Relative (g %) | 0.34±0.02 | 0.31±0.01 | 0.32±0.01 |
| Spleen | Absolute (g) | 0.62±0.05 | 0.55±0.02 | 0.57±0.02 |
| | Relative (g %) | 0.27±0.02 | 0.23±0.01 | 0.24±0.02 |
| Kidney | Absolute (g) | 1.32±0.06 | 1.49±0.09 | 1.56±0.19 |
| | Relative (g %) | 0.58±0.01 | 0.60±0.02 | 0.68±0.09 |
| Thymus | Absolute (g) | 0.60±0.04 | 0.34±0.04 | 0.52±0.06 |
| | Relative (g %) | 0.27±0.02 | 0.14±0.01** | 0.22±0.02 |
| Testes | Absolute (g) | 1.14±0.15 | 2.62±0.10 | 1.45±0.12 |
| | Relative (g %) | 0.50±0.06 | 1.00±0.04** | 0.60±0.07 |
| Seminal vesicle | Absolute (g) | 1.01±0.13 | 1.31±0.14 | 0.92±0.16 |
| | Relative (g %) | 0.45±0.07 | 0.50±0.06 | 0.38±0.08 |
| Prostate | Absolute (g) | 0.40±0.09 | 0.47±0.05 | 0.37±0.03 |
| | Relative (g %) | 0.18±0.04 | 0.19±0.03 | 0.15±0.01 |
| Uterus | Absolute (g) | 0.63±0.08 | 0.48±0.10 | 0.60±0.02 |
| | Relative (g %) | 0.28±0.03 | 0.21±0.04 | 0.27±0.01 |

The values are expressed as mean±SE (n = 6 animals/group). ** Statistically highly significant difference, $p$ <0.01 by ANOVA, followed by Dunnet's multiple comparison, as compared to control group.

The values for the biochemical parameters in treated and control rats are presented in Table 3. Blood glucose level and serum urea, alkaline phosphates, total protein, albumin and globulin level increased significantly; SGOT and SGPT activity decreased significantly in processed borax solution with a lower dose (22.5 mg/kg) treated rats. Serum urea, creatinine, bilirubin and total protein level increased significantly, and serum alkaline phosphates activity decreased significantly in processed borax solution with a higher dose (112.5 mg/kg) treated rats (as compared to control rats treated with the vehicle).

The effect of the processed borax solution on haematological parameters of experimental and control rats is presented in Table 4. The results indicate that all haematological parameters measured (haemoglobin, red cells indices, total leucocytes, % lymphocyte, % monocyte, % granulocyte, and platelets) remained within physiological range. However, % lymphocyte, % monocyte, and % granulocyte altered significantly in processed borax solution with a lower dose (22.5 mg/kg) treated rats (as compared to control rats treated with the vehicle).

In the histopathological study, no serious derangement in the cytoarchitecture of eight vital organs was seen in both of the dose levels of the test drug administered groups. Mild increase in cellularity in the cytoarchitecture of the spleen and very good spermatogenesis in the cytoarchitecture of testis observed in processed borax solution with a lower dose (22.5 mg/kg) treated rats. Glomerular dilatation in the cytoarchitecture of kidney and decrease in the spermatogenesis in the cytoarchitecture of testis were found in processed borax solution with a higher dose (112.5 mg/kg) treated rats (Plate 1a-d).

**Cardiac activity study**

The effective administration of the processed borax solution on heart rate, QRS complex, and time between two repolarisation of the heart of experimental and control rats is presented in Table 5. The data reveal no change to significant level in these parameters in both of the treated groups (22.5 and 112.5 mg/kg) in comparison to the vehicle control group.

Table 4—Effect of two dose levels of test drug by oral route on hematological parameters in Charles Foster albino rats treated consecutively for 30 days

| Parameters | Groups (Dose mg/kg) | | |
|---|---|---|---|
| | Control (--) | ST1 (22.5) | ST5 (112.5) |
| Hb (%) | 13.18±0.46 | 12.95±0.15 | 12.67±0.26 |
| RBC ($10^{12}$/L) | 7.04±0.22 | 6.99±0.13 | 6.93±0.25 |
| MCV (fL) | 80.50±0.92 | 80.35±0.40 | 81.82±0.60 |
| Haematocrit (%) | 48.50±1.33 | 47.16±0.84 | 46.25±2.03 |
| MCH (Pg) | 19.63±0.32 | 18.55±0.42 | 18.50±0.41 |
| MCHC (g/dL) | 33.42±0.48 | 32.50±0.24 | 32.62±0.39 |
| RDW (%) | 6.90±0.34 | 6.60±0.15 | 6.40±0.22 |
| TLC ($10^9$/L) | 1.86±0.20 | 2.38±0.32 | 2.40±0.38 |
| Lymphocyte (%) | 68.52±2.11 | 77.50±1.09** | 68.00±4.67 |
| Monocyte (%) | 3.47±0.17 | 2.50±0.22** | 4.10±0.28 |
| Granulocyte (%) | 27.98±2.03 | 20.00±1.21** | 27.90±4.48 |
| Platelet ($10^9$/L) | 698.00±134.99 | 599.67±030.70 | 988.33±180.79 |

The values are expressed as mean±SE (n = 6 animals/group). ** Statistically highly significant difference, $p$ <0.01 by ANOVA, followed by Dunnet's multiple comparison, as compared to control group.

Table 3—Effect of two dose levels of test drug by oral route on biochemical parameters in Charles Foster albino rats treated consecutively for 30 days

| Parameters | Groups (Dose mg/kg) | | |
|---|---|---|---|
| | Control (--) | ST1 (22.5) | ST5 (112.5) |
| Blood glucose (mg/dL) | 092.33±4.25 | 127.50±7.51** | 094.50±4.79 |
| Blood urea (mg/dL) | 29.50±3.31 | 41.17±2.65** | 41.50±1.99** |
| Serum creatinine (mg/dL) | 0.60±0.026 | 0.67±0.033 | 0.80±0.037** |
| Serum cholesterol (mg/dL) | 57.17±3.47 | 56.67±3.69 | 64.83±4.37 |
| Serum triglyceride (mg/dL) | 131.50±20.85 | 103.67±10.22 | 145.17±26.28 |
| Serum bilirubin (mg/dL) | 0.47±0.03 | 0.38±0.03 | 1.05±0.21** |
| Serum alkaline phosphatase (mg/dL) | 157.50±05.35 | 231.00±22.31** | 126.50±10.29 |
| SGOT (IU/L) | 338.17±52.49 | 131.00±15.09** | 425.67±89.03 |
| SGPT (IU/L) | 091.83±04.76 | 060.00±06.28** | 104.83±13.99 |
| Serum total protein (g/dL) | 7.18±0.15 | 8.85±0.19** | 7.77±0.16* |

The values are expressed as mean±SE (n = 6 animals/group). *, ** Statistically significant and highly significant difference, $p$ <0.05, $p$ <0.01 respectively by ANOVA, followed by Dunnet's multiple comparison, as compared to control group.

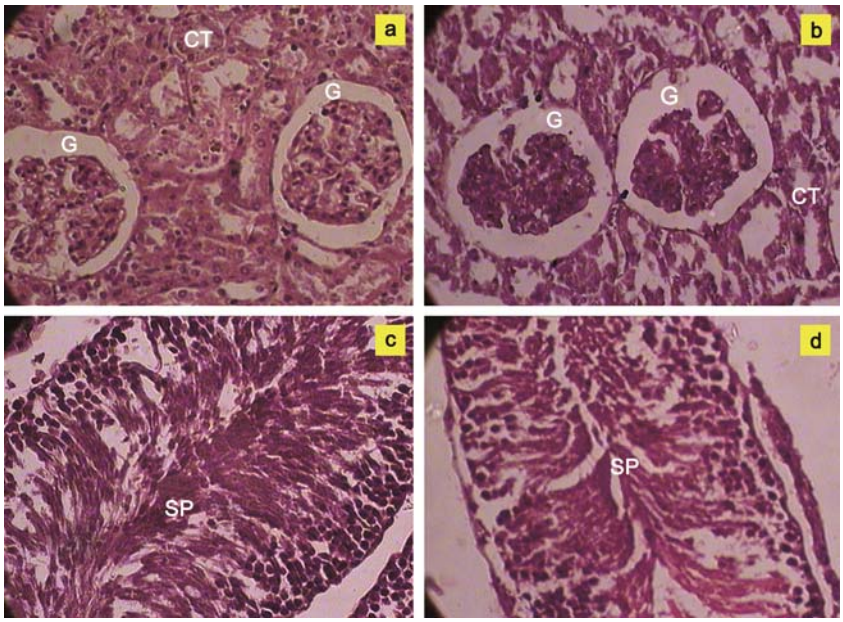


Plate 1—a) Histopathology of kidney from lower dose (22.5 mg/kg) treated group; b) Histopathology of kidney from higher dose (112.5 mg/kg) treated group; c) Histopathology of testis from lower dose (22.5 mg/kg) treated group, and d) Histopathology of testis from higher dose (112.5 mg/kg) treated group.

Table 5— Effect of two dose levels of test drug by oral route on cardiac activity parameters in Charles Foster albino rats treated consecutively for 30 days

| Parameters | Day | Groups (Dose mg/kg) | | |
|---|---|---|---|---|
| | | Control (--) | ST1 (22.5) | ST5 (112.5) |
| Heart rate (/min) | 1 | 403.33±29.97 | 389.50±20.91 | 399.83±26.64 |
| | 15 | 413.83±20.34 | 406.83±23.90 | 390.83±26.18 |
| | 30 | 406.83±23.90 | 395.00±16.44 | 379.00±17.57 |
| QRS complex (sec) | 1 | 0.083±0.003 | 0.086±0.007 | 0.087±0.004 |
| | 15 | 0.103±0.008 | 0.100±0.007 | 0.097±0.008 |
| | 30 | 0.093±0.007 | 0.097±0.008 | 0.103±0.008 |
| Repolarization time (sec) | 1 | 0.150±0.013 | 0.153±0.011 | 0.152±0.010 |
| | 15 | 0.145±0.007 | 0.148±0.009 | 0.152±0.007 |
| | 30 | 0.148±0.009 | 0.150±0.008 | 0.158±0.008 |

The values are expressed as mean±SE (n= 6 animals/group).

## Discussion

Borax can result in reproductive and developmental toxicity, neurotoxicity and acute toxicity[13,14]. There are many reports regarding the cytotoxicity of borax. In a study, the cytotoxicity of borax was studied in human fibroblasts and C3H/10T1/2 mouse embryo fibroblasts, which reported that 0.8 mg/mL borax concentration reduced cell growth and caused cytotoxicity[13]. Two recent studies have reported cytoprotective activity of processed borax on induced aconite poisoning in rats[2,3]. The route of borax absorption is important for human health risk assessment. The degree of borax toxicity depends on the doses or concentration that the human body receives. In an *in vivo* study of borax absorption, percutaneous absorption through the intact human skin was low and was significantly less than the average daily dietary intake[14]. The study also found that borax affected human cell growth. Developmental toxicity was found to be more likely than other toxicity due to borax[15].

The results of the acute toxicity study indicate that processed borax by the oral route with the doses up to 1.8 mg/kg did not produce any sign of toxicity or death in rats, suggesting a $LD_{50}$ above 1.8 mg/kg by oral route. According to Weir and Fisher, the $LD_{50}$ values for borax are 4.5 g/kg and 4.98 g/kg in males and females Sprague-Dawley rats respectively[16]. Acute

toxicity of borax was performed in the present study because no acute toxicity of processed (dehydrated) borax is reported. And no acute toxicity or death due to borax treatment observed in the present study may be due to processing (dehydration treatment) of borax. Likewise, subacute treatment showed that processed borax at doses of 22.5 and 112.5 mg/kg/day during 30 days did not produce any deaths or clinical signs of toxicity. Besides, the body weight, water and food intake were not altered during the treatment period.

The blood glucose level was increased significantly in a lower dose (22.5 mg/kg) treated rats. The high occurrence of *Diabetes mellitus* was reported in some communities across borate centres in Turkey[17]. Borax causes developmental toxicity and impaired energy metabolism leads to hyperglycaemia. In lower dose (22.5 mg/kg) treated rats, a huge increase in serum urea level was observed but increase in serum creatinine level was marginal indicate impairment in urea production due to hepatocellular toxicity or due to chronic infections. Decreased serum bilirubin, SGOT and SGPT activity and normal hepatic cytoarchitecture could rule out the presence of and hepatocellular involvement so that the elevated urea level may be due to existing chronic infection. A high increase in serum urea level along with a highly significant increase in serum creatinine level observed in higher dose (112.5 mg/kg) treated rats reveals the occurrence of renal toxicity; glomerular dilatation found in the cytoarchitecture of the kidney in this group supports this phenomenon. These results also support the previously reported kidney toxicity caused by borax and boron compounds[18]. Significantly elevated serum bilirubin level increased SGOT and SGPT level, and significantly decreased serum alkaline phosphates activity found in higher dose (112.5 mg/kg) treated rats reveal the existence of chronic hepatocellular disorders due to the administration of test drug in higher dose level.

The red cell count and red blood cell indices were not affected by both of the dose levels of the test drug. All the changes were marginal in comparison to control group. So it should be considered that the test drug does not have any adverse effect on the red blood cells physiology. The changes in the differential count of WBC are the indicative existence of chronic inflammation in lower dose (22.5 mg/kg) treated rats. Both of the dose levels of the test drug did not affect the platelet count to significance level; suggest the test drug has no pathological effect on platelet development.

Body weight indicates health status of any living being. So here increase in body weight in albino rats indicate normal progressive health status of the animals, and it is also indicative of the fact that no degenerative changes are occurring during the test drug administration. So increase in body weight could suggest that there is no harmful effect of the test drug on body function as a whole. However, in a previous study body weight decrease by boric acid treatment in mice was reported[19].

The weight of thymus decreased significantly in lower dose (22.5 mg/kg) treated rats and decreased in higher dose (112.5 mg/kg) treated rats, which indicate degenerative changes in the thymus. In a recent study, numerous apoptotic lesions in the thymus caused by borax in Wistar rats was reported, which support the changes in the present study[20].

Mild increase in cellularity in the cytoarchitecture of the spleen, significant increase in weight of testis and very good spermatogenesis in the cytoarchitecture of the testis observed in lower dose (22.5 mg/kg) administered group should be considered as good effect of the test drug in that dose level. Glomerular dilatation in the cytoarchitecture of kidney, reduction in weight of testis and decrease in the spermatogenesis in the cytoarchitecture of testis found in higher dose (112.5 mg/kg) treated rats reveals the occurrence of some pathological changes in kidney and testis due to the administration of higher dose level of the test drug. The findings are supportive to the previous report of male reproductive toxicity caused by the administration of borax[16]. Borax caused testicular degeneration in dogs, including spermatogenic arrest and atrophy of the seminiferous epithelium of the tubules[15].

No change in the parameters of ECG is conclusive of exclusion of any pathological intervention of the processed borax on the heart in rats.

## Conclusion

The acute and sub-acute oral administration of processed borax did not induce serious alterations in almost all haematological, ponderal, and histopathological parameters in Charles Foster albino rats. However, changes observed in many biochemical parameters are indicative of the treated borax *per se* may produce functional changes in many organs. Further, moderate toxicity with processed borax in 5 folds of therapeutic effective dose (5×TED) was seen in the kidney. It can be recommended from the observed result that the

processed borax has no cardiac toxicity; it should be prescribed in therapeutic dose only and should be careful to the patients with renal dysfunction.

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