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# Effect of Acute and Sub-Acute Toxicity Study on Siddha Pediatric Polyherbal Formulation Maantha Kiyaazham

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**Keywords:** Maantha kiyaazham, Siddha, Children, Respiratory disease, toxicity, Nilavembu, Seendhil, Adhathodai

**ABSTRACT**

Respiratory illness is one of the major health issues of the pediatric age group, particularly in the toddler stage. *Maantha kiyaazham* (MK) is the polyherbal formulation given in the Indian traditional Siddha medical system and specified for children's respiratory and gastrointestinal problems. As per OECD guidelines Acute and sub-acute toxicity studies were carried out in MK to evaluate the safety profile.MK was administered orally to rats daily for 14 days to study acute toxicity and for 28 days in different doses such as 100mg and 200mg to study sub-acute toxicity. Hematological, biochemical, necropsy and histopathological analyses were done in rats elaborately and observation was done properly. The hematological and biochemical analysis did not show any significant change in blood parameters. In histopathological analysis also no toxic manifestations were seen in any animal's kidney, heart, liver, and brain. Thus, this study revealed that no characteristic clinical signs of toxicity were seen and Siddha drug Maantha kiyaazham. Hence it is authenticated, and the investigational drug is safe for humans.

## INTRODUCTION:

Our India has many traditional medical systems. Among them, Siddha is very ancient and classic. The interventional drug Maantha kiyaazham's (MK)preparation has been given in the "Kannusamiyam parambarai vaithiyam" book and quoted for respiratory and gastrointestinal issues (Maantham) of children.MK includes seven herbs such as asAdhathodai *(Justicia adhatoda),* Seenthil Kodi (*Tinospora cordifolia),* and Kandankathiri *(Solanum xanthocarpum*), Sukku *(Zingiber officinale),* Pei pudal (*Trichosanthes cucumerina),* Parpadagam (*Mollugo cerviana),* Nilavembu *(Andrographis paniculata).* As per Siddha literature, most of the above drugs have Anti-inflammatory, Antispasmodic, Carminative, and Immunomodulator activity. Nowadays children are facing many health troubles due to their low immunity. The illness is caused by different viruses and bacteria. In children, respiratory diseases are more extensive than in adults. The highest number of infections occur during the first three years of life. To develop the children's mental and physical health many solutions are given in Siddha medical science without producing many side effects. To evaluate the safety of the investigational drug, preclinical studies are essential.

## MATERIALS AND METHODS

### COLLECTION AND AUTHENTICATION

The ingredients of Maantha Kiyaazham were procured from a local drug shop in Chennai. The raw materials were identified and authenticated by Siddha Central Research Institute, Chennai-106.

### PURIFICATION AND PREPARATION

The adulterants from the raw drugs were removed, cleaned, and dried in shade. The purified ingredients were coarsely ground up to become decoction powder. The herbal decoction was prepared as per the procedure mentioned in the Kannusamiyam parambarai vaithiyam book.

## AIM:

The study aims to evaluate the acute and sub-acute toxicity of the siddha polyherbal formulation "Maantha kiyaazham".

**ANIMALS:**

Healthy three female Wistar rats weighing 220-250gm were used for the acute toxicity study. Three groups of six Wistar rats were used for subacute toxicity. Each group includes three male rats and three female rats weighing around 220-250gm. The animals were procured from the animal house of C.L Baid Metha college of pharmacy, Chennai – 97 with the approval of the Institute Animal Ethical Committee (IAEC). The approval No: IAEC/XL/08/CLBMCP/2013 dated 31.08.2013. They were fed with a balanced standard pellet diet and water. Maintained under standard laboratory conditions, provided optimal light cycle.

**ACUTE ORAL TOXICITY STUDY:**

An acute oral toxicity test of Maantha kiyaazham was carried out as per OECD guideline 423. The test substance is administered in a single dose by gavage using a stomach tube for 14 days. General behavior, respiratory pattern, cardiovascular signs, motor activities, reflexes, defecation, urination change in skin, fur, and body weight were monitored daily. After 14 days no mortality rate was observed.

**TABLE 1 OBSERVATION OF RAT'S BEHAVIOURAL SIGNS**

| **Group** | **Day** |
|---|---|
| Bodyweight | Normal |
| Assessments of posture | Normal |
| Signs of Convulsion<br>Limb paralysis | Absence of sign (-) |
| Body tone | Normal |
| Lacrimation | Absence |
| Salivation | Absence |
| Change in skin color | No significant color change |
| Piloerection | Not observed |
| Defecation | Regular Solid consistency |
| Sensitivity response | Normal |
| Locomotion | Occasional loose stools |
| Muscle grip ness | Normal |
| Rearing | Normal |
| Urination/Color | Slightly turbid |

**SUB- ACUTE ORAL TOXICITY STUDY:**

Sub-acute toxicity of test drug Maantha kiyaazham was carried out as OECD guideline – 407 for 28 days. The trial drug was administered in low doses and high doses. Group 1 received distilled water and served as normal control. Group 2 received 100mg per kg Maantha kiyaazham and Group 3 received 200mg per kg Maantha kiyaazham. The body weight and food consumption of the animals were evaluated periodically. At the end of the 28$^{th}$ day, they were fastened overnight and blood samples were obtained. The animals were observed for gross changes and signs of sub-acute toxicity in all systems of the body for 28 days.

**TABLE 2 FOOD INTAKE AND BODY WEIGHT OF RATS EXPOSED TO MAANTHA KIYAAZHAM**

| **CONTROL** | **Food (g/day/rat)** | **Bodyweight (g)** |
|---|---|---|
| Mean | 24 | 232.2 |
| Std. Deviation | 2.757 | 4.07 |
| Std. Error | 1.125 | 1.662 |
| **LOW DOSE** | **Food (g/day/rat)** | **Body weight (g)** |
| Mean | 23.83 | 235.2 |
| Std. Deviation | 0.9832 | 2.994 |
| Std. Error | 0.4014 | 1.222 |
| **HIGH DOSE** | **Food (g/day/rat)** | **Body weight (g)** |
| Mean | 26.33 | 231.7 |
| Std. Deviation | 1.966 | 2.944 |
| Std. Error | 0.8028 | 1.202 |

**TABLE 3 EFFECT OF TEST DRUG ON HEMATOLOGICAL AND BIOCHEMICAL ANALYSIS**

| **CONTROL** | **Total red cells count (×10 6 µl)** | **Total WBC count (×10 3 µl)** | **Platelet count (×10 3 µl)** | **Packed cell volume (%)** | **MCV (fl)** | **MCH (pg)** | **MCHC (g/dl)** | **Blood sugar® (mg/dl)** | **BUN (mg/dl)** |
|---|---|---|---|---|---|---|---|---|---|
| Mean | 7.5 | 10 | 541.7 | 56.17 | 66 | 31.67 | 40.17 | 83 | 20 |
| Std. Deviation | 1.378 | 2.28 | 32.5 | 3.061 | 3.406 | 3.83 | 4.119 | 6.033 | 4.382 |
| Std. Error | 0.5627 | 0.9309 | 13.27 | 1.249 | 1.39 | 1.563 | 1.682 | 2.463 | 1.789 |
| **LOW DOSE** | **Total red cells count (×10 6 µl)** | **Total WBC count (×10 3 µl)** | **Platelet count (×10 3 µl)** | **Packed cell volume (%)** | **MCV (fl)** | **MCH (pg)** | **MCHC (g/dl)** | **Blood sugar® (mg/dl)** | **BUN (mg/dl)** |
| Mean | 6.667 | 9 | 529 | 53 | 63.17 | 30.5 | 45 | 82.33 | 20 |
| Std. Deviation | 1.751 | 1.549 | 37.43 | 9.675 | 5.193 | 4.135 | 4.733 | 7.711 | 3.742 |
| Std. Error | 0.7149 | 0.6325 | 15.28 | 3.95 | 2.12 | 1.688 | 1.932 | 3.148 | 1.528 |
| **HIGH DOSE** | **Total red cells count (×10 6 µl)** | **Total WBC count (×10 3 µl)** | **Platelet count (×10 3 µl)** | **Packed cell volume (%)** | **MCV (fl)** | **MCH (pg)** | **MCHC (g/dl)** | **Blood sugar® (mg/dl)** | **BUN (mg/dl)** |
| Mean | 7.833 | 11.17 | 544.2 | 53 | 60.83 | 31 | 43 | 85.67 | 19.83 |
| Std. Deviation | 1.602 | 1.169 | 19.28 | 5.865 | 7.574 | 5.06 | 6.87 | 3.204 | 3.764 |
| Std. Error | 0.654 | 0.4773 | 7.872 | 2.394 | 3.092 | 2.066 | 2.805 | 1.308 | 1.537 |

**TABLE 4 EFFECT OF TEST DRUG ON HAEMOGLOBIN BLOOD LEUKOCYTE COUNT**

| **CONTROL** | **HB (g/dl)** | **Neutrophils (%)** | **lymphocytes (%)** | **eosinophils (%)** | **monocytes (%)** | **basophils (%)** |
|---|---|---|---|---|---|---|
| Mean | 16 | 73.83 | 31.67 | 1.5 | 2.517 | 0.3333 |
| Std. Deviation | 1.265 | 3.43 | 1.366 | 0.3688 | 3.229 | 0.5164 |
| Std. Error | 0.5164 | 1.4 | 0.5578 | 0.1506 | 1.318 | 0.2108 |
| **LOW DOSE** | **HB (g/dl)** | **Neutrophils (%)** | **lymphocytes (%)** | **eosinophils (%)** | **monocytes (%)** | **basophils (%)** |
| Mean | 15.33 | 75.5 | 35.17 | 1.717 | 1.2 | 0.3333 |
| Std. Deviation | 0.8165 | 3.017 | 3.971 | 0.4792 | 0.5831 | 0.5164 |
| Std. Error | 0.3333 | 1.232 | 1.621 | 0.1956 | 0.238 | 0.2108 |
| **HIGH DOSE** | **HB (g/dl)** | **Neutrophils (%)** | **lymphocytes (%)** | **eosinophils (%)** | **monocytes (%)** | **basophils (%)** |
| Mean | 15.67 | 74 | 34.33 | 1.483 | 2.4 | 0.3333 |
| Std. Deviation | 1.633 | 2.53 | 5.61 | 0.2994 | 3.254 | 0.5164 |
| Std. Error | 0.6667 | 1.033 | 2.29 | 0.1222 | 1.328 | 0.2108 |

**TABLE 5 EFFECT OF TEST DRUG ON SERUM CREATININE AND LIPID PROFILE**

| **CONTROL** | **Serum creatinine (mg/dl)** | **Serum total cholesterol (mg/dl)** | **Serum triglycerides level (mg/dl)** | **Serum HDL cholesterol (mg/dl)** | **Serum LDL cholesterol (mg/dl)** | **Serum VLDL cholesterol (mg/dl)** | **Serum total protein (g/dl)** |
|---|---|---|---|---|---|---|---|
| Mean | 1.05 | 102 | 50.83 | 26.5 | 52 | 36.83 | 8.983 |
| Std. Deviation | 0.3728 | 4 | 4.875 | 5.683 | 5.762 | 3.189 | 2.554 |
| Std. Error | 0.1522 | 1.633 | 1.99 | 2.32 | 2.352 | 1.302 | 1.043 |
| **LOW DOSE** | **Serum creatinine (mg/dl)** | **Serum total cholesterol (mg/dl)** | **Serum triglycerides level (mg/dl)** | **Serum HDL cholesterol (mg/dl)** | **Serum LDL cholesterol (mg/dl)** | **Serum VLDL cholesterol (mg/dl)** | **Serum total protein (g/dl)** |
| Mean | 0.7333 | 99.67 | 45.83 | 23.33 | 52.67 | 36.17 | 7.55 |
| Std. Deviation | 0.216 | 4.633 | 4.167 | 2.805 | 3.327 | 2.639 | 2.694 |
| Std. Error | 0.08819 | 1.892 | 1.701 | 1.145 | 1.358 | 1.078 | 1.1 |
| **HIGH DOSE** | **Serum creatinine (mg/dl)** | **Serum total cholesterol (mg/dl)** | **Serum triglycerides level (mg/dl)** | **Serum HDL cholesterol (mg/dl)** | **Serum LDL cholesterol (mg/dl)** | **Serum VLDL cholesterol (mg/dl)** | **Serum total protein (g/dl)** |
| Mean | 0.9667 | 100.7 | 50.5 | 26.83 | 53.17 | 38.17 | 8.833 |
| Std. Deviation | 0.4082 | 6.154 | 5.01 | 3.656 | 5.879 | 4.262 | 3.312 |
| Std. Error | 0.1667 | 2.512 | 2.045 | 1.493 | 2.4 | 1.74 | 1.352 |

**TABLE 6 EFFECT OF TEST DRUG ON SERUM ENZYME AND PROTEIN**

| **CONTROL** | **Serum albumin (g/dl)** | **SGOT (AST) (IU/ml)** | **SGPT (ALT) (IU/L)** |
|---|---|---|---|
| Mean | 3.967 | 124.3 | 66 |
| Std. Deviation | 1.134 | 15.29 | 5.514 |
| Std. Error | 0.4631 | 6.243 | 2.251 |
| **LOW DOSE** | **Serum albumin (g/dl)** | **SGOT (AST) (IU/ml)** | **SGPT (ALT) (IU/L)** |
| Mean | 4.117 | 123.7 | 66.5 |
| Std. Deviation | 1.167 | 6.022 | 5.612 |
| Std. Error | 0.4764 | 2.459 | 2.291 |
| **HIGH DOSE** | **Serum albumin (g/dl)** | **SGOT (AST) (IU/ml)** | **SGPT (ALT) (IU/L)** |
| Mean | 5.167 | 121.2 | 68 |
| Std. Deviation | 1.941 | 4.75 | 6.387 |
| Std. Error | 0.7923 | 1.939 | 2.608 |

**HISTOPATHOLOGICAL STUDY**

**NECROPSY:**

All rats were sacrificed after the blood collection. The positions shapes, sizes, and colors of internal organs were evaluated. The kidney, liver, heart, lungs, spleen, pancreas, brain, ovaries, and testis tissues were excised from all rats and a histopathological assessment was done.

**TABLE 7 EFFECTS OF TEST DRUG ON ORGANS MORPHOLOGY**

| GROUPING | KIDNEY | LIVER | HEART | LUNGS | SPLEEN | PANCREAS | BRAIN | OVARIES | TESTIS |
|---|---|---|---|---|---|---|---|---|---|
| GROUP I-CONTROL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL |
| GROUP II-LOW DOSE | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL |
| GROUP III-HIGH DOSE | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL | NORMAL |

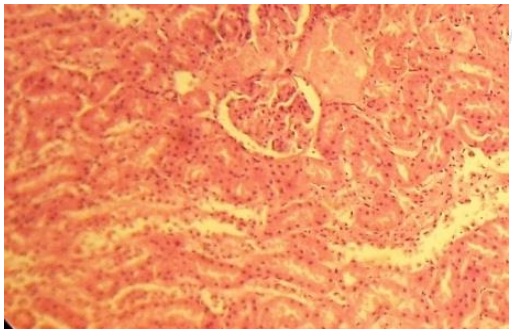
**HISTOPATHOLOGICAL ANALYSIS OF SUB-ACUTE TOXICITY STUDY**

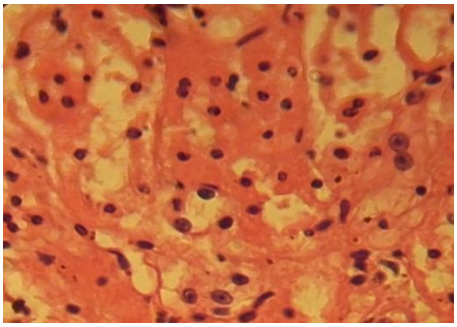
**SAMPLE: KIDNEY**

**MAGNIFICATION:**

**LOW POWER 10X** **HIGH POWER 45X**

GROUP: CONTROL GROUP GROUP: CONTROL GROUP





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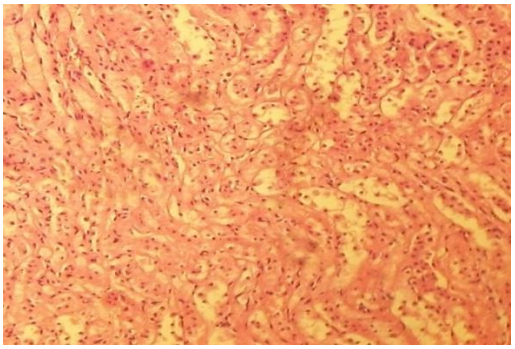

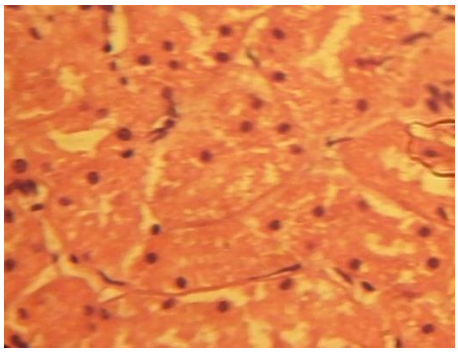

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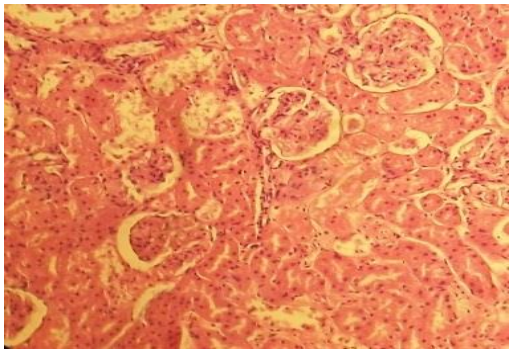

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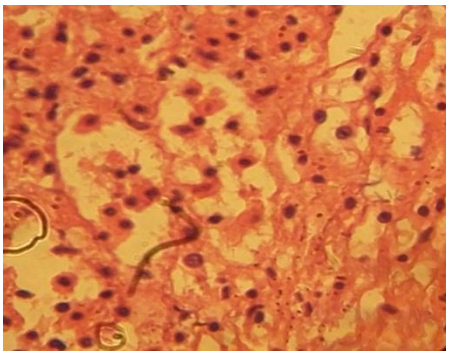
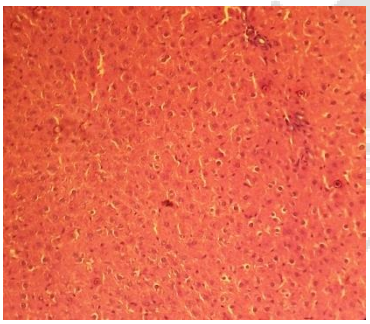


**SAMPLE: LIVER**

**MAGNIFICATION:**

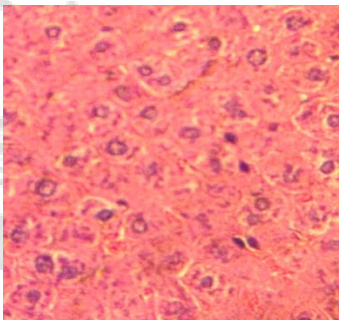
**LOW POWER 10X**

GROUP: CONTROL GROUP



**HIGH POWER 45 X**

GROUP: CONTROL GROUP



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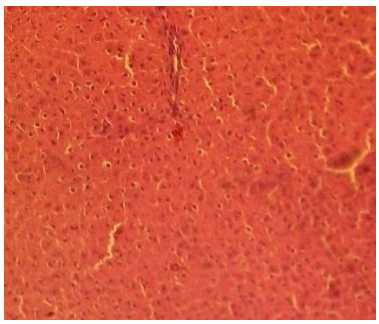

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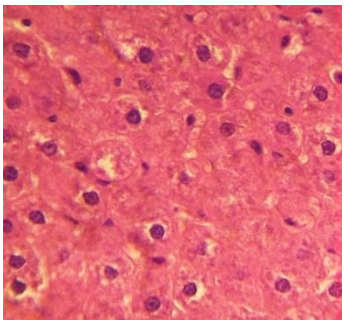

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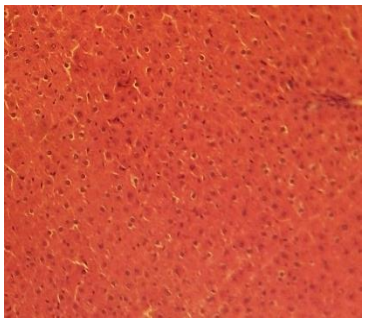
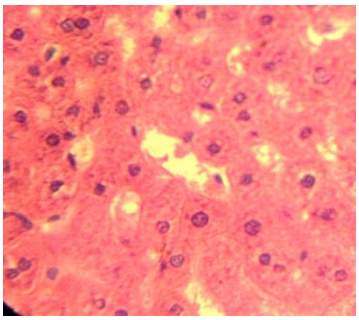
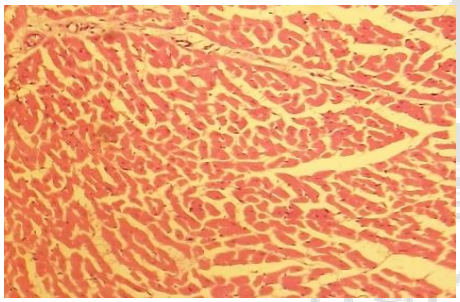
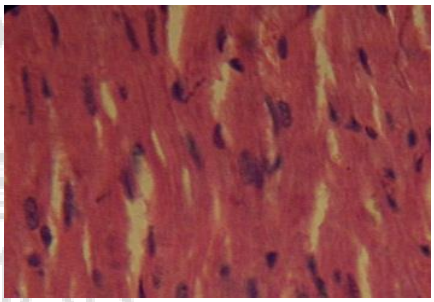



**SAMPLE: HEART**

**MAGNIFICATION:**

**LOW POWER 10X** **HIGH POWER 45 X**

GROUP: CONTROL GROUP GROUP: CONTROL GROUP

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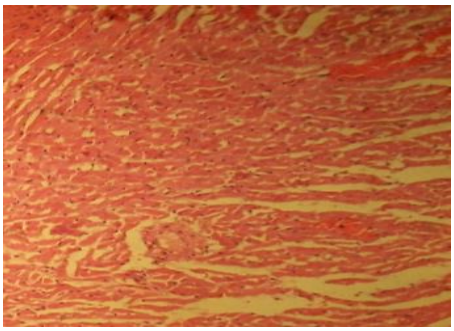
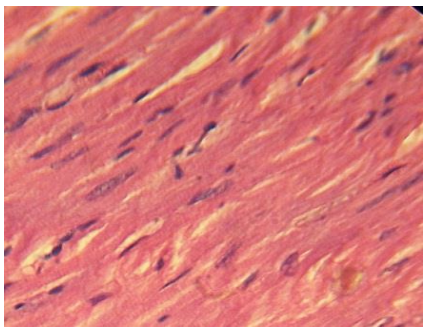

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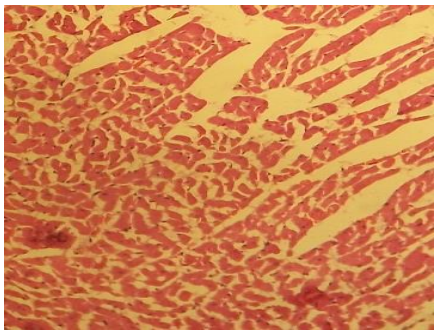
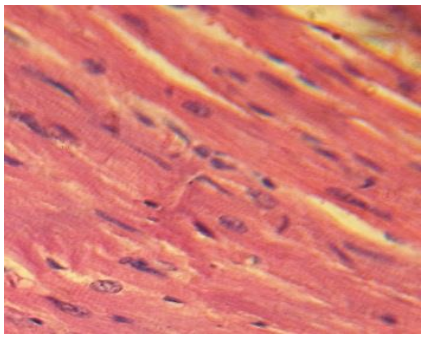

**SAMPLE: BRAIN**

**MAGNIFICATION:**

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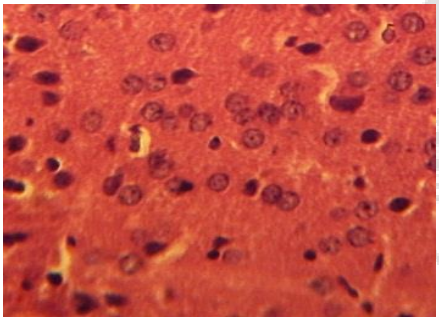
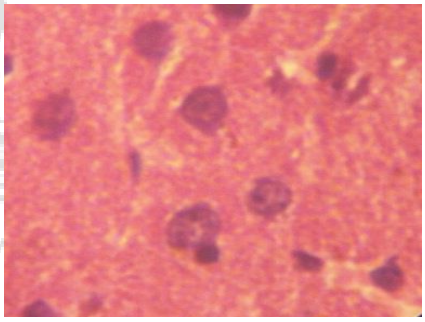
GROUP: CONTROL GROUP GROUP: CONTROL GROUP

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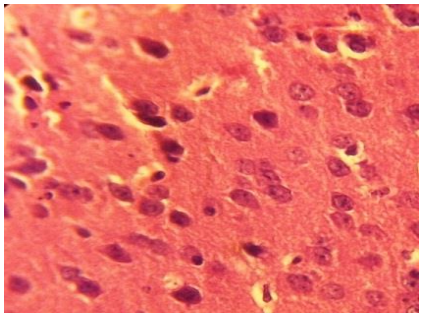
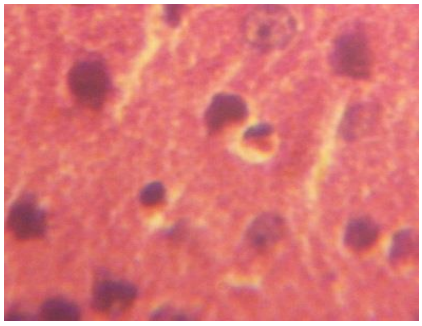

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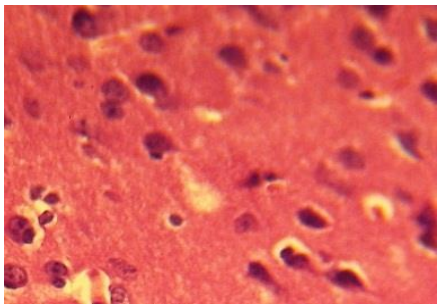
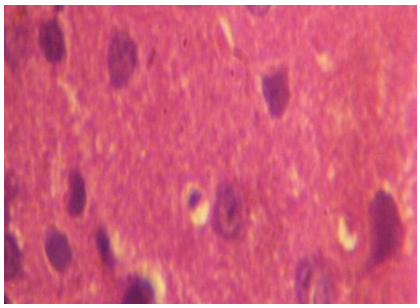

**STATISTICAL ANALYSIS:**

The statistical analysis was carried out using the one-way analysis of variance (ANOVA) method. P values < 0.05 were considered significant.

**RESULTS:**

All the animals from control and tested survived throughout the toxicity study period of 28 days. No signs of toxifications were observed in both animals groups (lower dose and higher dose). No signs of behavioral changes or hematological and biochemical abnormalities were observed. The gross pathological examination did not show any abnormality.

**HISTOPATHOLOGICAL REPORT**

| **Sample** | **Observation** |
|---|---|
| Kidney | The distal tubule and Lumen of the kidney appear normal in all the three groups<br>The appearance and arrangement of a nephrotic bundle in all three groups are also normal.<br>The renal cortex and medulla appear normal<br>The arrangement of nephrotic bundles appears regular and highly intact |
| Heart | Cardiac myocyte appears larger with regular fiber length.<br>The nuclear arrangement was linear and appears normal no signs of content leakage<br>Myocardial cells appear with intact and prominent nuclei with no major signs of abnormalities in all three groups. |
| Liver | No signs of vacuolar degeneration.<br>The Hepatic Parenchymal lining appears normal |

| | |
|---|---|
| | The arrangement of hepatocytes was intact with prominent nuclei stained.<br>Hepatic veins appear normal.<br>No signs of necrosis or cirrhosis.<br>No signs of inflammation in all three groups. |
| Brain | No signs of hemorrhage and apoptosis<br>No signs of edema and Inter-neuronal distance appears regular with no signs of degeneration.<br>No signs of ischemic brain tissue damage in all three groups |

## CONCLUSION:

Based on the above findings, no toxic effects were noticed in general observation, body weight and food consumption, hematological and biochemical analysis, histopathological study up to 200mg/kg of body weight of Maantha Kiyaazham administered via oral route over 28 days. So this study concluded that Maantha kiyaazham is safe and suitable for therapeutic use in humans.

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