**Scholars Academic Journal of Pharmacy (SAJP)** **ISSN 2320-4206 (Online)**
**Sch. Acad. J. Pharm., 2017; 6(11): 454-459** **ISSN 2347-9531 (Print)**

(An International Publisher for Academic and Scientific Resources)
www.saspublisher.com

# Evaluation of Toxicity Profiles of Siddha Metallic Preparation of '*Aya Chendooram'* In Laboratory Animals

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**Original Research Article**

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**Article History**
*Received: 15.11.2017*
*Accepted: 22.11.2017*
*Published:30.11.2017*

**DOI:**
*10.21276/sajp.2017.6.11.2*

**Abstract:** Ayachendooram (AC), a widely used Siddha metallic preparation consist of purified iron fillings, vinegar and odina bark juice. The formulation was evaluated for acute and chronic toxicity in rats with reference to histopathological, haematological, and bio chemical parameters and detection of iron from the various tissues of rats. During acute toxicity study, there were no any adverse effects found in the general behaviour and mortality at any dose level given. In chronic toxicity studies (90days) Ayachendooram in various dose level (18, 90, and 180 mg/kg B.wt) did not cause any changes in hematological and biochemical parameters with exception of a transient rise in uric acid, albumin, SGOT and lymphocyte level. The changes observed were significant only at the highest dosage of 180 mg/kg B.wt. Excepting albumin level, which increased with average dose (90mg), which was not significant when compared to control. Feed and water intake failed to reveal any marked changes in chronic toxicity studies. Histopathological lesions were non-specific in all organs between treated and control group except in liver revealed mild changes with highest dose level. In the present study the drug possessed no toxic effect upto 180 mg.
**Keywords:** Ayachendooram, uric acid, albumin, histopathology, acute and chronic toxicity.

## INTRODUCTION

The Healing Dimension revealed by the Siddhas is called as 'Siddha medicine'. In the Indian subcontinent, the systems of Siddha represent the ancient traditional systems of medicine. Siddha is nearly 10,000 years old, as recognized by the Indian government and other researchers of south Indian antiquity.

There is popular saying in Tamil Nadu 'Virunthum Marunthum moonru naal', meaning 'The feast and medicine is only for three days'. It indicates that the ancient Tamil people found relief from disease in only three days. So, Siddha medicine can work fast and effectively in its Pharmaco-dynamic properties. Depending on the situation, on the disease and on the person's constitution, Siddha medicine is classified as 'emergency medicine' or 'course medicine' [1]. "Treat with roots and leaves. If it does not respond Then administer parpam and chendooram" The term *Chendooram* is applied to the metals, minerals and animal products. This ayachendooram preparation is mainly used for Iron deficiency anaemia, Insufficiency of seminal secretions, Spermatorrhaea, premature ejaculation and Ascites and rheumatism [2]. The composition of ayachendooram individually has pharmcodynamic importance. Iron has for long been considered important for the body. Lauha Bhasma (calcined iron) has been used in ancient Indian medicine. Iron was used for weakness, which is common in anaemia. In 1713 iron was shown to be present in blood. [3]. The most obvious clinical result of iron deficiency is anaemia, and the only indication for therapy with iron is to provide material for haemoglobin synthesis [4]. The bioavailability of iron in the colon increased by prebiotic and synbiotic diets [5], it is mainly stored in liver and spleen in the form of ferretin is used to meet the daily requirements not provided by the diet. Nearly all cells contain ferritin, the ferritin will release the $Fe^{+++}$ to circulating blood to meet their deficiency, aggregated ferritin referred to as haemosiderin [4]. The iron influenced so many important functions of the body. Iron has reported to have synthesis of Myoglobin, it is the single-chain hemoprotein in cytoplasm that increases the rate of diffusion of dioxygen from capillary red cells to cytoplasm and mitochondria. The concentration of myoglobin in skeletal muscle is drastically reduced (40–60%) in tissue due to iron deficiency, thus limiting the rate of diffusion of dioxygen from erythrocytes to mitochondria [6]. The deficiency of iron leads to

Trypanosoma cruzi infection in host [7], affecting cognition and learning processes in humans [8], significant alterations in the metabolism of 5-hydroxytryptamine in brain [9] and reduction in γ-aminobutyric acid (GABA) and glutamic acid content of the brain. On rehabilitation with the iron-supplemented diet for 1 week, these decreased enzyme activities in brain attained the corresponding control values [10]. Vinegar Reported that have anti-hypertensive and antiglycemic effect. The anti-hypertensive activity was due to reductions in both plasma renin activity and plasma aldosterone concentrations [11] and antiglycemic effect clinically proved by [12]. *Odina wodier, roxb.*, family *anacardiceae* is a large tall tree found in deciduous forest in india, srilanka, china, Malaysia and Philippine island [13] it is popularly known as kashmala, odomaram, jiol in local language and in English it is called rhus olina [14]. It contains carbohydrate and reducing sugar. Traditionally the various parts of this plants are used for many disorder and the leaves of the plant used for elephantiasis [14], juice used as emetic, bark powder used as tooth powder, bark extract has been reported to be useful in vaginal trouble, ulcer, heart disease and gum obtained from the plant used as tablet binder [15]. Siddha system of medicine has many preparations for the treatment of Anaemia. Out them '*Aya chendooram*' is one of the best medicine which is widely used by the Siddha expert to counteract the anaemia in the patients. However, the information available on the safety profile of this preparation is scanty. Hence, evaluate the safety of this preparation the present study was under taken with following objective.

To evaluate the acute toxicity in rats, 90 days repeated dose administration of *Aya Chendooram* in rats and estimate the levels of Iron in serum and various body organs after 90 days repeated dose administration in rats.

## MATERIAL AND METHODS

### Experimental animals

All the animals used in the present study were procured from the animal house of Pharmacology Department, Central Research Institute for Siddha, Chennai. The study was conducted after obtaining Institutional Animal Ethical committee Clearance (Proposal No.34/PHARMA/CRIS, 2007).

### Accommodation

The rats were housed in the polypropylene cages with paddy husk as bedding and with stainless steel top grill having facilities for providing food and drinking water in polypropylene bottles with stainless steel sipper tube. The animals were housed in air conditioned rooms [23-30$^0$C, Humidity (50-60-%)].

### Animal Identification

All animals were housed individually with appropriate identification (label) on cages. Animal in each cage was identified by standard dye marking and by the labels on the cage.

### Diet and water

The rats were maintained on standard pellet diet (Amrut Laboratory Animal Feed, Nav Maharastra House, Pune, Maharastra) and purified water (by Aqua guard) in polypropylene bottles. The animals had free access to feed and water.

### Day and night cycle

Twelve hourly light and dark cycle were maintained.

### Drugs and Chemicals

Ayachendooram was obtained from SKM Laboratories, Chennai, a GMP certified laboratory**.** All the other chemicals used were of analytical grade.

### Acute Toxicity

Twenty four (12 Male and 12 Female) Albino mice, weighing approximately 18-25g were used for the study. The acute toxicity study was carried out as per Guidelines for Ayurveda and Siddha drugs. Healthy mice of either sex were selected and grouped into four comprising of six animals in each group. The animals were fasted for four hours prior to the study with free access to water. The test drug was suspended in the honey and given in graded doses up to maximum dose level. One group received honey only, which served as control. The animals were observed for any toxic manifestations and mortality for 72 hours. There after animals were observed for 14 days. [16]

### Chronic Toxicity

The Wister rats ranging between 135-145 gms for males and 120-130 gms for females were selected for the present study. A total of twenty four Wistar rats (12 Males + 12 Females) were randomized and equally divided into four groups comprising six animals in each. The Group I, II & III received the AC therapeutic dose, five times the therapeutic dose, and ten times the therapeutic dose (18mg/kg, 90mg/kg and 180mg/kg) respectively for 90 days daily (*ccras.nic.in)*. Control group animal received honey. The animals were observed for pre-terminal morbidity and mortality and examined clinically. Clinical biochemical and hematological investigations were carried out. This was followed by euthanization and histopathological examination of various organs which includes liver, spleen, kidneys, lungs, heart, intestine, ovaries, testes, and stomach. [16]

### Statistical methods

The statistical analysis was performed by the difference between the groups tested by one-way analysis of variance (ANOVA), $P< 0.05$ was considered to be statistically significant.

## RESULTS

### Acute Toxicity

The test drug and vehicle were administered to mice as per the guidelines, under close observation for 4 hrs and followed by daily observation for 14 days, produced neither behavioural changes nor mortality and morbidity in all the groups of animals. Hence further investigation planned.

### Chronic Toxicity

### Body Weight and Feed Intake

No significant changes were observed in the body weight and feed in take in 90 days treatment in all the three dose level when compared to control. The growth rate was linear in all the treated groups when compared to control (Table 1.1-1.4).

**Table-1.1: Effect of Ayachendooram on feed in take (gm) in rats**

| Groups | Day 0 | Day 7 | Day 14 | Day 21 | Day 28 | Day 35 | Day 42 |
|---|---|---|---|---|---|---|---|
| Control | 9.17 ± 0.95$^{a}$ | 10.33 ± 0.74$^{a}$ | 11.02 ± 0.69$^{a}$ | 9.76 ± 0.66$^{a}$ | 10.54 ± 0.28$^{a}$ | 12.62 ± 0.48$^{a}$ | 11.12 ± 0.65$^{a}$ |
| Group I | 9.20 ± 0.89$^{ab}$ | 8.43 ± 0.50$^{b}$ | 10.83 ± 0.67$^{a}$ | 9.85 ± 0.81$^{a}$ | 10.09 ± 0.89$^{a}$ | 12.78 ± 1.18$^{a}$ | 11.14 ± 1.41$^{a}$ |
| Group II | 9.00 ± 1.16$^{b}$ | 9.50 ± 0.38$^{a}$ | 10.62 ± 0.41$^{a}$ | 11.68 ± 0.60$^{a}$ | 12.23 ± 0.99$^{a}$ | 11.28 ± 1.38$^{a}$ | 11.33 ± 0.93$^{a}$ |
| Group III | 9.15 ± 0.89$^{a}$ | 8.09 ± 0.42$^{b}$ | 10.14 ± 0.29$^{a}$ | 10.12 ± 0.38$^{a}$ | 10.33 ± 0.52$^{a}$ | 10.78 ± 0.72$^{a}$ | 9.78 ± 0.41$^{a}$ |

Means bearing different superscript differ significantly (P < 0.05)

**Table-1.2: Effect of ayachendooram on feed in take (gm) in rats**

| Groups | Day 49 | Day 56 | Day 63 | Day 70 | Day 77 | Day 84 | Day 91 |
|---|---|---|---|---|---|---|---|
| Control | 11.14 ± 0.33$^{a}$ | 11.59 ± 0.25$^{a}$ | 10.83 ± 0.66$^{a}$ | 10.40 ± 0.37$^{a}$ | 9.99 ± 0.27$^{a}$ | 12.28 ± 0.55$^{a}$ | 11.19 ± 0.54$^{a}$ |
| Group I | 10.88 ± 1.43$^{a}$ | 11.31 ± 1.19$^{a}$ | 13.33 ± 1.12$^{a}$ | 11.43 ± 0.92$^{a}$ | 10.45 ± 0.85$^{a}$ | 13.00 ± 1.26$^{a}$ | 12.33 ± 1.31$^{a}$ |
| Group II | 11.07 ± 0.72$^{a}$ | 11.83 ± 0.77$^{a}$ | 10.88 ± 0.59$^{a}$ | 12.31 ± 1.02$^{a}$ | 12.19 ± 0.96$^{a}$ | 13.26 ± 1.01$^{a}$ | 13.00 ± 1.08$^{a}$ |
| Group III | 10.19 ± 0.47$^{a}$ | 10.47 ± 0.83$^{a}$ | 12.38 ± 0.51$^{a}$ | 11.35 ± 0.71$^{a}$ | 10.31 ± 1.14$^{a}$ | 13.07 ± 0.92$^{a}$ | 12.16 ± 0.77$^{a}$ |

Means bearing different superscript differ significantly (P < 0.05)

**Table-1.3: Effect of Ayachendooram on body weight (gm) in rats**

| Groups | Day 0 | Day 7 | Day 14 | Day 21 | Day 28 | Day 35 | Day 42 |
|---|---|---|---|---|---|---|---|
| Control | 112.50 ± 3.59$^{a}$ | 118.83 ± 2.71$^{a}$ | 132.67 ± 6.04$^{a}$ | 148.33 ± 7.38$^{a}$ | 155.00 ± 8.85$^{a}$ | 161.67 ± 9.28$^{a}$ | 165.00 ± 10.08$^{a}$ |
| Group I | 108.17 ± 7.47$^{a}$ | 127.50 ± 8.04$^{a}$ | 146.67 ± 10.22$^{a}$ | 149.17 ± 14.23$^{a}$ | 154.17 ± 13.13$^{a}$ | 167.33 ± 15.99$^{a}$ | 176.33 ± 17.67$^{a}$ |
| Group II | 110.83 ± 3.75$^{a}$ | 125.83 ± 4.55$^{a}$ | 139.17 ± 5.69$^{a}$ | 158.33 ± 7.49$^{a}$ | 160.83 ± 10.28$^{a}$ | 164.50 ± 11.87$^{a}$ | 180.83 ± 13.32$^{a}$ |
| Group III | 95.33 ± 1.67$^{a}$ | 115.00 ± 3.16$^{a}$ | 128.00 ± 4.58$^{a}$ | 140.00 ± 3.87$^{a}$ | 154.00 ± 5.87$^{a}$ | 159.33 ± 7.61$^{a}$ | 167.83 ± 7.79$^{a}$ |

Means bearing same superscripts do not differ significantly (P < 0.05)

**Table-1.4: Effect of Ayachendooram on body weight (gm) in rats**

| Groups | Day 49 | Day 56 | Day 63 | Day 70 | Day77 | Day 84 | Day 91 |
|---|---|---|---|---|---|---|---|
| Control | 163.33 ± 12.02$^{a}$ | 170.00 ± 11.26$^{a}$ | 172.50 ± 13.53$^{a}$ | 178.33 ± 15.58$^{a}$ | 181.67 ± 16.36$^{a}$ | 182.50 ± 16.01$^{a}$ | 189.17 ± 16.09$^{a}$ |
| Group I | 188.33 ± 20.07$^{a}$ | 193.00 ± 20.36$^{a}$ | 197.50 ± 21.98$^{a}$ | 207.83 ± 22.75$^{a}$ | 204.33 ± 23.48$^{a}$ | 216.67 ± 26.92$^{a}$ | 219.17 ± 27.33$^{a}$ |
| Group II | 189.50 ± 15.34$^{a}$ | 205.00 ± 16.07$^{a}$ | 201.67 ± 17.97$^{a}$ | 210.83 ± 17.53$^{a}$ | 224.17 ± 20.18$^{a}$ | 224.17 ± 21.66$^{a}$ | 227.50 ± 22.20$^{a}$ |
| Group III | 178.33 ± 8.43$^{a}$ | 178.33 ± 9.10$^{a}$ | 180.83 ± 10.04$^{a}$ | 191.67 ± 10.85$^{a}$ | 193.33 ± 16.26$^{a}$ | 200.00 ± 15.44$^{a}$ | 207.33 ± 16.43$^{a}$ |

Means bearing same superscripts do not differ significantly (P < 0.05)

**Clinical Biochemistry**

Toxicity studies for 90 days with 180 mg dose level showed significant difference in uric acid level when compared to control. No significant changes were observed in Group I and II. Group II showed significant variation in albumin level compared to Group I and III but no significant to control. The serum glutamate level in Group III revealed significantly difference when compared to control, Group I and II. It is represented in the table1.5-1.6.

**Table-1.5: Effect of Ayachendooram on Biochemical Parameters in rats**

| Groups | Sugar | Urea | Creatinine | Uric acid | T.P | Albumin |
|---|---|---|---|---|---|---|
| Control | 70.00 ± 6.25$^{a}$ | 42.83 ± 1.74$^{a}$ | 0.80 ± 0.03$^{a}$ | 0.77 ± 0.21$^{a}$ | 7.03 ± 0.38$^{a}$ | 3.13 ± 0.07$^{ab}$ |
| Group I | 74.50 ± 4.33$^{a}$ | 39.00 ± 2.11$^{a}$ | 0.80 ± 0.03$^{a}$ | 1.20 ± 0.21$^{ab}$ | 7.13 ± 0.27$^{a}$ | 2.85 ± 0.13$^{a}$ |
| Group II | 71.83 ± 7.84$^{a}$ | 35.50 ± 2.41$^{a}$ | 0.75 ± 0.02$^{a}$ | 0.93 ± 0.13$^{ab}$ | 7.47 ± 0.48$^{a}$ | 3.42 ± 0.11$^{b}$ |
| Group III | 72.33 ± 4.77$^{a}$ | 38.83 ± 3.79$^{a}$ | 0.80 ± 0.03$^{a}$ | 1.68± 0.24$^{b}$ | 7.25 ± 0.47$^{a}$ | 2.97 ± 0.11$^{a}$ |

Means bearing different superscript differ significantly (P < 0.05)

**Table-1.6: Effect of Ayachendooram on Biochemical Parameters in rats**

| Groups | Globulin | Bilirubin | A.L.P | SGOT | SGPT |
|---|---|---|---|---|---|
| Control | 3.90 ± 0.35$^{a}$ | 0.41 ± 0.09$^{a}$ | 126.67 ± 13.87$^{a}$ | 187.67 ± 11.02$^{b}$ | 48.83 ± 2.39$^{a}$ |
| Group I | 4.28 ± 0.25$^{a}$ | 0.40 ± 0.02$^{a}$ | 189.50 ± 20.81$^{a}$ | 136.17 ± 15.40$^{a}$ | 58.00 ± 3.33$^{a}$ |
| Group II | 4.05 ± 0.57$^{a}$ | 0.37 ± 0.06$^{a}$ | 179.17 ± 18.49$^{a}$ | 156.00 ± 8.41$^{ab}$ | 58.83 ± 6.19$^{a}$ |
| Group III | 4.45 ± 0.35$^{a}$ | 0.37 ± 0.05$^{a}$ | 188.67 ± 22.58$^{a}$ | 250.67 ± 12.57$^{c}$ | 66.67 ± 5.70$^{a}$ |

Means bearing different superscript differ significantly (P < 0.05)

**Hematology**

Haematological data showed that the lymphocytes level was significant in between Group III and Group I, but these levels were found to be non significant when compared to control and Group II. And all other parameters remained normal without any significant difference in both control and treated Groups (Shown in table 1.7-1.8).

**Table-1.7: Effect of Ayachendooram on Haematological Parameters in rats**

| Groups | PCV | Hb(g%) | MCHC(%) | TC(%) | Neutrophil(%) | Lymphocyte(%) |
|---|---|---|---|---|---|---|
| Control | 44.18 ± 1.32$^{a}$ | 15.52 ± 0.50$^{a}$ | 35.10 ± 0.26$^{a}$ | 5616.67 ± 423.81$^{a}$ | 51.50 ± 1.98$^{a}$ | 47.67 ± 2.25$^{ab}$ |
| Group I | 41.97 ± 0.84$^{a}$ | 14.78 ± 0.35$^{a}$ | 35.28 ± 0.44$^{a}$ | 5766.67 ± 495.76$^{a}$ | 55.67 ± 4.90$^{a}$ | 43.50 ± 5.20$^{a}$ |
| Group II | 41.48 ± 1.11$^{a}$ | 14.67 ± 0.31$^{a}$ | 35.40 ± 0.32$^{a}$ | 6316.67 ± 786.31$^{a}$ | 39.83 ± 3.15$^{a}$ | 54.83 ± 2.24$^{ab}$ |
| Group III | 41.10 ± 1.05$^{a}$ | 14.47 ± 0.36$^{a}$ | 35.20 ± 0.17$^{a}$ | 6316.67 ± 742.71$^{a}$ | 43.17 ± 2.15$^{a}$ | 58.17 ± 2.76$^{b}$ |

Means bearing different superscript differ significantly (P < 0.05)

**Table-1.8: Effect of Ayachendooram on Haematological Parameters in rats**

| Groups | Monocyte (%) | Eosinophil (%) | Basophil (%) | Platelets | RBC (10/mm) | MCV (Cu µ) | MCH (µg) |
|---|---|---|---|---|---|---|---|
| Control | 0.33 ± 0.21$^{a}$ | 0.33 ± 0.21$^{a}$ | 0 | 3.97 ± 0.25$^{a}$ | 5.15 ± 0.16$^{a}$ | 85.82 ± 0.85$^{a}$ | 29.95 ± 0.13$^{a}$ |
| Group 1 | 0.33 ± 0.21$^{a}$ | 0.50 ± 0.22$^{a}$ | 0 | 3.89 ± 0.32$^{a}$ | 4.95 ± 0.12$^{a}$ | 84.78 ± 0.92$^{a}$ | 29.82 ± 0.14$^{a}$ |
| Group 2 | 0.17 ± 0.17$^{a}$ | 0$^{a}$ | 0 | 4.49 ± 0.33$^{a}$ | 4.88 ± 0.10$^{a}$ | 85.47 ± 1.38$^{a}$ | 30.00 ± 0.07$^{a}$ |
| Group 3 | 0.17 ± 0.17$^{a}$ | 0.17 ± 0.17$^{a}$ | 0 | 4.31 ± 0.27$^{a}$ | 4.78 ± 0.12$^{a}$ | 85.88 ± 0.26$^{a}$ | 30.20 ± 0.13$^{a}$ |

Means bearing different superscript differ significantly (P < 0.05)

**HISTOPATHALOGICAL STUDIES**

The highest dose of ayachendooram shows dcogestion and degeneration of hepatocytes in liver, the all other organs histological studies shows normal archytexture between treated and control groups.

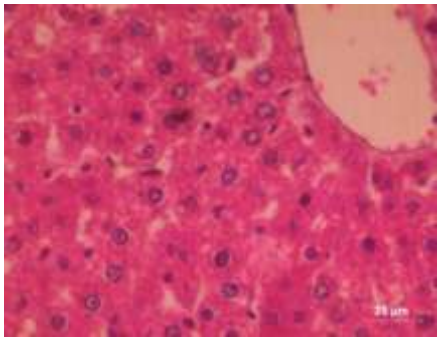

**Fig-1: Photomicrograph of liver-Control**

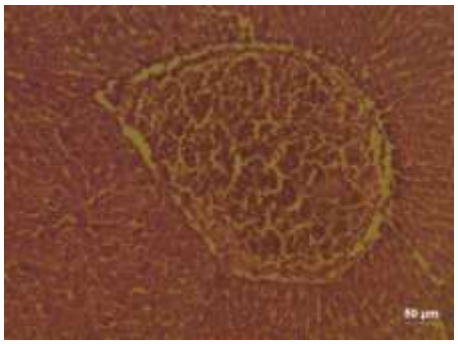

**Fig-2: Photomicrograph of liver-treated with Ayachendooram (highest dose) showing congestion and degeneration of hepatocytes**

## DISCUSSION

In acute toxicity study, there was no mortality observed upto maximum dose level of A.C administered orally. Thus our test suggested that A.C does not cause any apparent acute toxicity. This test in rats was undertaken based on the report on non-lethality of animals in acute (mice) toxicity studies. The changes in body weight have been used as indicator of adverse effect of A.C. [17]. Since there were no changes in animal behaviour and body weights at all the doses of treated groups when compared to control. The present result suggests that the oral administration of A.C is non toxic. There were no pre terminal deaths in animals receiving therapeutic dose, five times the therapeutic dose and ten times the therapeutic dose. The food intake were significantly different between groups exposed to test compound Group II, Group III and control on $0^{th}$ and $7^{th}$ day, but no gain in animal body weight at the same day, this may be due to normal physiological changes.

The bio chemical parameter such as uric acid, SGOT, and albumin level in serum increased with GroupIII and Group II respectively, all other parameters remained normal. The SGOT is good indices of liver and kidney damage than SGPT [18]. Elevated levels of SGOT with Group III showed mild Histopathological changes in liver. The albumin is the one of the most important plasma protein, maintain the osmotic pressure of blood [19] and prevent the escape of fluids from blood to tissue hence, indirectly maintain the blood volume and blood pressure and it is synthesized by liver. The decreased albumin level called Hypoalbunaemia is also an indication of liver damage. The increased albumin level was significant between treated group and non significant to control. Our data revealed albumin level was normal in all treated and control groups [20]. And a histopathological examination of kidney in treated Groups shows normal compared to control animals. So from the above statement increased SGOT level does not caused marked changes in liver. The raised uric acid level has been observed with impairment of renal function [21]. In the present study significant increase in uric acid level at highest dose of AC treated group manifest non-hazardous effect. In humans and higher primates, uric acid is the final oxidation (breakdown) product of purine metabolism and is excreted in urine. In most other mammals, the enzyme Uricase further oxidizes uric acid to allantoin [22]. So the increased uric acid level may be due to decreased uricase or high purine metabolism by the composition of formulation. Uric acid may be a marker of oxidative stress, [23] and may have a potential therapeutic role as an antioxidant [24]. On the other hand, like other strong reducing substances such as ascorbate, uric acid can also act as a prooxidant [25]. AC increase the lymphocyte level in highest dose once but these level significant to Group I and non significant to control and Group II. The increased level of lymphocyte with high dose of AC emphasizes the advantageous effect in immune system. From the haematological results, the normal haemoglobin level in all groups shows iron may not involved in haemoglobin synthesis in normal humans. In the blood iron ($Fe^{3+}$) bound to a glycoprotein $beta_1$ globulin known as transferrin. In this form it is carried to the storage

depots (liver, spleen, bone marrow), and stored as a ferritin, from where it is utilized for erythropoiesis [4].

## CONCLUSION

In conclusion, AC can be considered safe with reference of above result of acute and 90 days toxicity studies with parameter of feed intake, body weight and biochemical and hematological. Further, the composition of formulation has some additional pharmacological properties these results substantiate the beneficial effect of formulation. From the above results proved that Ayachendooram was safety for long term use at various dose levels.

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