



## Effect of *Aloe vera* Juice on the Toxicity Induced by Ethionamide and Para Amino Salicylic Acid on Histological Alterations in Sprague-Dawley Rats

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### ABSTRACT

Fresh *Aloe vera* plant leaves were brought from botanical garden and sample was identified and brought to the laboratory in the Department of Zoology, Patkar-Varde College, Goregaon (W), Mumbai. 50 grams of leaves were then grounded with 50ml of distilled water in sterilized pestle and mortar. The yield was being calculated based on weight of the extract compared to the weight of the pulp of the leaves. Forty eight (48) *Sprague-dawley* rats (average weight 150 - 250 g) of either sex were used for the experiment. The drugs ETH and PAS drug and *Aloe vera* juice were given to respective groups daily for 28 days. At the end of study animals were dissected and various tissues/ glands were processed for their histological studies. From the histology study, it was found that the anti-tuberculosis drugs ETH and PAS induced toxicity in male and female *Sprague-dawley* rats by disturbing the histological structure from minimal to mild changes in the histoarchitecture of lungs, Heart and Kidneys of male and female *Sprague-dawley* rats either independently or in combination. It was also found that when the anti-tuberculosis drugs ETH and PAS co-administered with *Aloe vera* juice found amelioration of the histoarchitecture of lungs, Heart and Kidneys of male and female *Sprague-dawley* to normal. It was also found that, the rats treated with ETH and PAS drugs independently or in combination with *Aloe vera* juice, no histoarchitectural changes were observed in Brain, Pancreas, Spleen, testes, and ovaries of rat. Thus, it confirms the antioxidant, anti-inflammatory and free scavenging property of *Aloe vera* juice to protect the histological structures of the different organs and glands of *Sprague-dawley* rat.

**Keywords:** *Aloe vera*, ETH, PAS, Histoarchitecture, Rats, Organs, glands.

### INTRODUCTION

**M**ycobacterium tuberculosis is the infectious agent that causes tuberculosis (TB). Despite medical advances, tuberculosis remains fatal and is the leading cause of human death in many countries. Every second person in the world is infected with tuberculosis. The estimated number of new cases of tuberculosis every year around the world is around 9.6 million. Approximately one-third of the world's population is currently infected with tuberculosis and up to 10% of these will develop active TB, causing 1.6 million deaths per year<sup>1</sup>. It has been studied that the development of MDR-TB is due to misuse of proper antibiotic treatment by patients and lack of attention focused on these patients. The very high incidence of MDR-TB has led to the use of second-line tuberculosis drugs.

Ethionamide (eth eye on a mid) is the most commonly used drug which shares similarities with Isoniazid in terms of structure and anti-mycobacterial function. The daily oral dose of Ethionamide is 250 mg/kg and can be increased to 1 gram if well tolerated by the patient. Some cases of ethionamide-induced hepatotoxicity have been severe and harmful cases have also been reported<sup>2</sup>. Para-aminosalicylic acid (PAS) was the first antibiotic found to be effective in the treatment of tuberculosis in the 1940s<sup>3</sup>. PAS treatment is uncommon and highly drug-resistant strains have limited resistance to this drug. Thus, PAS became the principal second-line agent for the treatment

of MDR-TB<sup>4</sup>. Hepatotoxicity is one of the most frequent and serious adverse effects of anti-TB drugs and can reduce treatment effectiveness by compromising treatment regimens<sup>5,6</sup>.

Several medicinal plants used traditionally for thousands of years are present in the herbal preparations of the Indian traditional health care system. Today, about 80% of the world population depends on botanical agents as medicines to meet their health issues<sup>7</sup>. In developing countries, traditional plant remedies are widely used to treat various diseases. Many varieties of plants have been used to treat a variety of diseases. More than 500 species of aloe are known, but *Aloe vera* is recognized as the "true *Aloe vera*" for its widespread use and purported healing powers<sup>8</sup>. *Aloe vera* has been used for many centuries for its medicinal and therapeutic properties. Aloe juice has been used for centuries as a laxative and medicinal cleanser<sup>9</sup>. Many of the health benefits associated with *Aloe vera* are attributed to promoting wound healing, antifungal activity, hypoglycemic or antidiabetic effects, and anti-inflammatory, anticarcinogenic, immunomodulatory, and gastroprotective properties<sup>10</sup>.

### MATERIALS AND METHODS

#### a) Collection and Identification:

Fresh *Aloe vera* plant leaves were brought from botanical garden and sample was identified and brought to the laboratory in the Department of Zoology, Patkar-Varde



College, Goregaon (W), Mumbai. *Aloe vera* plant identified by reviewing the literature and the final identification and authentication was done at Department of Botany, St Xavier's College (autonomous) Mumbai, India.

#### b) Preparation of Crude Extract:

Fresh *Aloe vera* leaves were rinsed 2-3 times in the tap-water. 50 grams of leaves were then grounded with 50ml of distilled water in sterilized pestle and mortar. The yield will be calculated based on weight of the extract compared to the weight of the pulp of the leaves in a sterile container and keep at -20 °C till further use.

#### c) Purchase of drugs

The drug ETH (Ethionamide) (Macleods Pharmaceuticals Ltd) and PAS (Para-aminosalicylic acid) (Lupin Ltd) were purchased following the Prescription of Physician by the medical practitioner, from New Krishna Medicos, Shop No. 3, Salim Estate Near Times Square, opposite Kanakia Seven, Marol, Andheri, (E), Mumbai, India.

#### d) Experimental Design

Forty eight (48) *Sprague-dawley* rats (average weight 150 - 250 g) of either sex were used for the experiment. They were purchased and procured from the National Toxicological Centre, APT Testing & Research Pvt. Ltd. (ATR) Pune. The experimental study was approved by Ethical committee at APT Research Foundation, Pune prior to the experimentation (CPCSEA NO. RP 01/2223 dated 11/June/2022). The animals were acclimatized, maintained and housed in APT laboratory for a week. The controlled humidity and temperature at 22+3°C, humidity 50-60 %, and illumination cycle set to 12-hlight/12 hrs dark cycle was also maintained. Six rats per cage were housed in polypropylene cages with stainless steel grill top, facilities for commercial Pallet food and water bottle with ad-libitum, and bedding of clean paddy husk.

**Table 1:** Showing dose level of *Aloe vera*, ETH and PAS in different groups of *Sprague-dawley* rats

Groups (n=6)	Treatment
Group-1	Animals fed with rat pellets and ordinary water
Group -2	ETH(132 mg/kg, p.o) for 28 days
Group -3	PAS( 400 mg/kg, p.o) for 28 days
Group -4	ETH (132 mg/kg, p.o) + PAS ( 400 mg/kg, p.o) for 28 days
Group -5	ETH (132 mg/kg, p.o) + <i>Aloe vera</i> juice (50 ml/kg, p.o) for 28 days
Group -6	PAS (400 mg/kg, p.o) + <i>Aloe vera</i> juice (50 ml/kg, p.o) for 28 days
Group -7	ETH (132 mg/kg, p.o)+ PAS( 400 mg/kg, p.o)+ <i>Aloe vera</i> juice (50 ml/kg, p.o) for 28 days
Group -8	Only <i>Aloe vera</i> juice (50 ml/kg, p.o) for 28 days

#### e) Administration of Test Article

The test article at the above concentration was administered to each rat by a single oral gavage. The animals were dosed using a stainless steel intubation needle fitted onto a suitably graduated syringe. The dosage volume administered to individual rat was adjusted according to its most recently recorded body weight. Animal weights were determined weekly along with food consumption. Animals were randomly divided into following groups containing 6 animals (3 males and 3 females) in each group. Test drug and inducers were given to respective groups as indicated in the table daily for 28 days. At the end of study various issues/ glands dissected and the tissues were (Lungs, Heart and Kidneys, Brain, Pancreas, Spleen, testes, and ovaries of rat) process for their histological studies.

#### f) Histological analysis

The liver tissue was dissected out and fixed in 10% formalin, dehydrated in gradual ethanol (50–100%), cleared in xylene, and embedded in paraffin. Five micron thick sections were prepared and then stained with hematoxylin and eosin (H–E) dye for photomicroscopic observation, including cell necrosis, fatty degenerative changes, hyaline regeneration, ballooning degeneration as proposed by <sup>11</sup> and histological structure of Lungs, Heart and Kidneys, Brain, Pancreas, Spleen, testes, and ovaries tissues were examined under the Biological digital microscope Motic B1 Series.

### RESULTS AND DISCUSSIONS

**Photograph 1 (A- H):** Showing Effect of *Aloe vera* Juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Lung of Male and Female *Sprague-dawley* rats.

**Group- A: NC (Normal Control):** In normal control male rats, histomorphological features of bronchi and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed. In normal control female rats, histomorphological features of bronchi and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed.

**Group- B: Animals treated with ETH:** In male rats, mild congested vascular tissue in the lung parenchyma was noted. Mild changes in alveolar pathological changes observed. The alveolitis and mononuclear inflammatory cellular (MNC) infiltration in the alveolar parenchyma was noted. The multifocal area shows giant alveoli. The emphysema in alveolar parenchyma was also noted. In female rats, a focal congested vessel in the lung parenchyma was observed. Focal infiltration of mononuclear cells in the interstitial space between alveolar walls was noted. The normal histomorphological features of bronchi and alveolar tissue with intact cellular details of the normal bronchiolar epithelium observed.

**Group- C: Animals treated with PAS:** In male rats, the mild focal congested vessels in the lung parenchyma were



noted. There was focal infiltration of mononuclear cells in the interstitial space between alveolar walls observed. The normal histomorphological features of bronchi and alveolar tissue with intact cellular details was found. In female rats, histomorphological features of bronchi and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed.

**Group- D: Animals treated with ETH + PAS:** In male rats, a minimal focal congested vessel in the lung parenchyma was noted. The mild focal infiltration of mononuclear cells in the interstitial space between alveolar walls was noted. Normal histomorphological features of bronchi and alveolar tissue with intact cellular details. In female rats, normal histomorphological features of bronchi and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed.

**Group- E: Animal treated with ETH+ Aloe vera juice:** In male rats, histomorphological features of bronchi and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed. In female rats, histomorphological features of bronchi and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed.

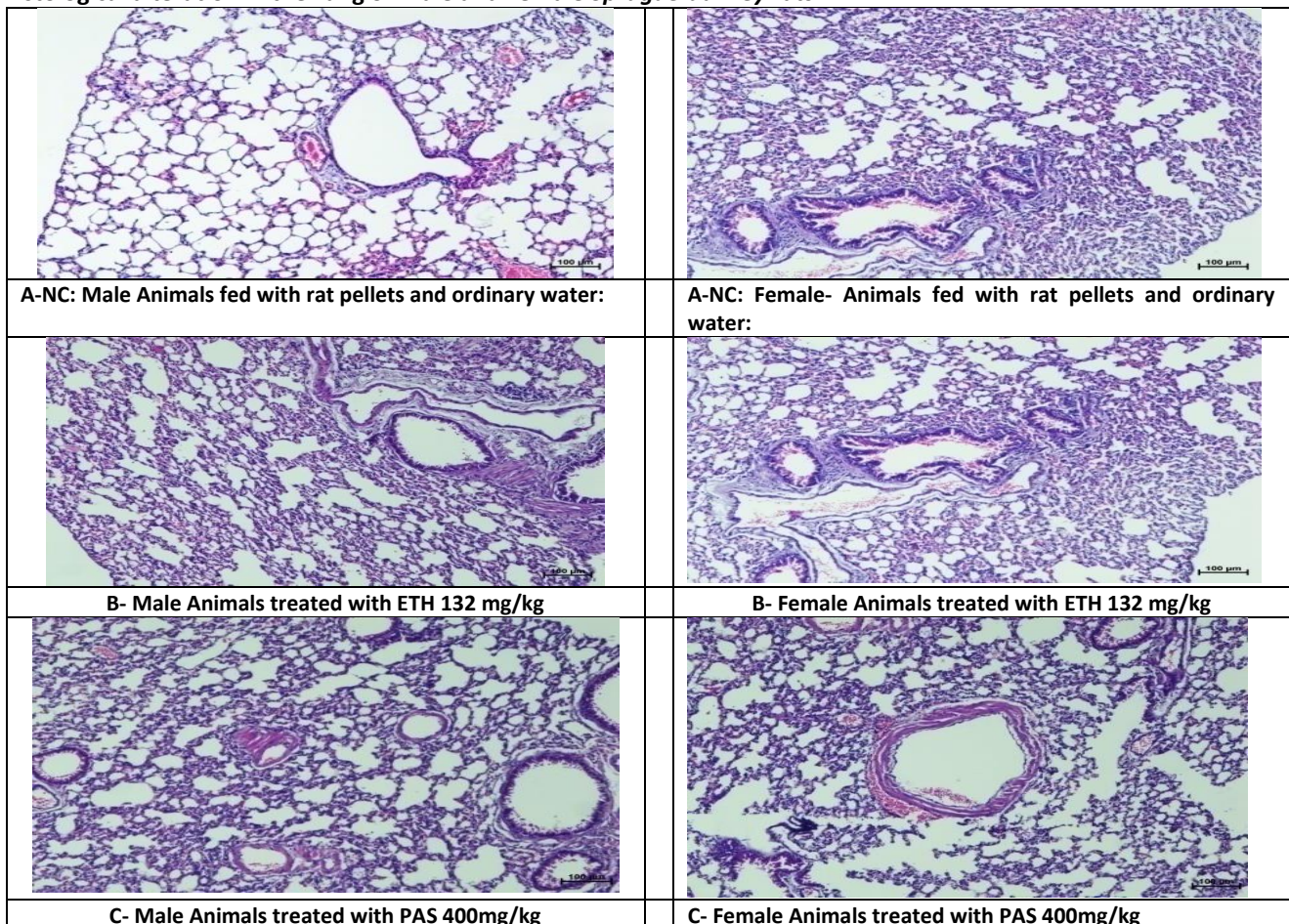
**Group- F: Animal treated with PAS +Aloe vera juice:** In male rats, normal histomorphological features of bronchi

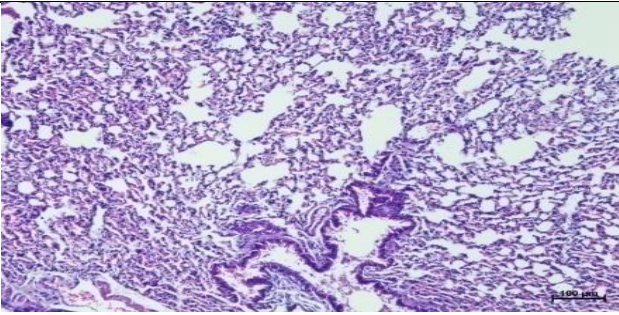
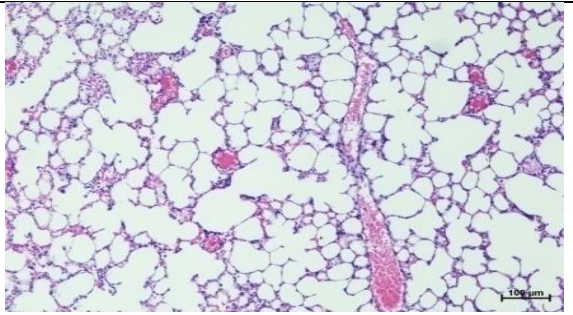
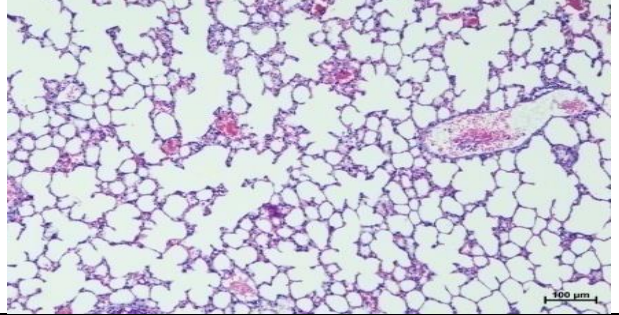
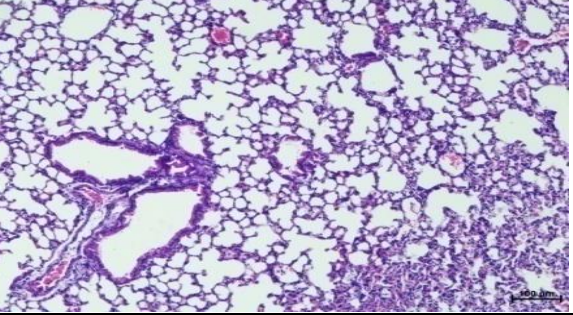
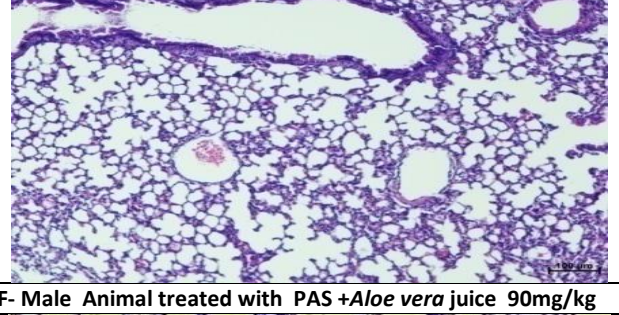
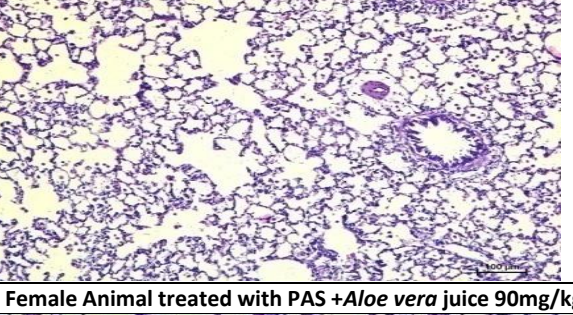
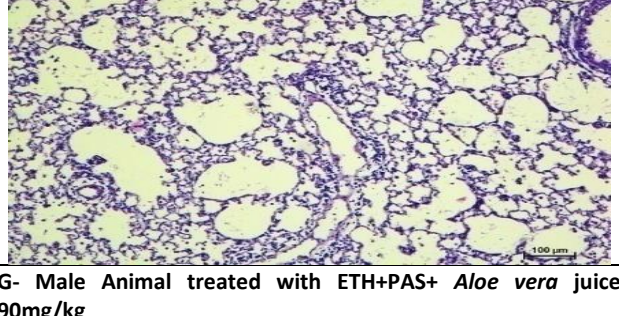
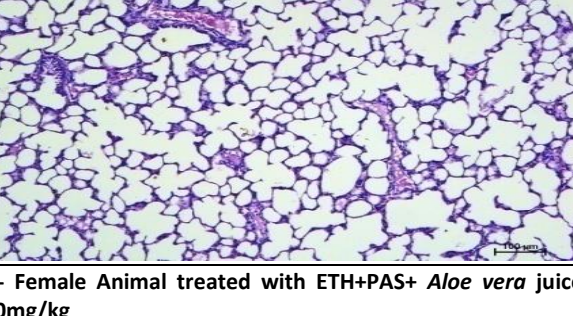
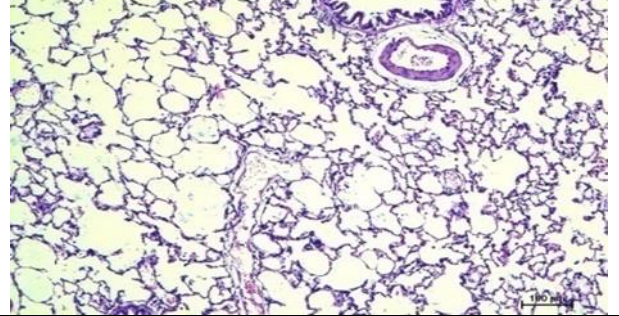
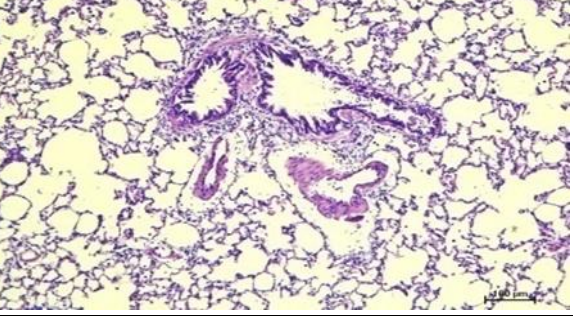
and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed. In female rats, the minimal focal congested vessel in the lung parenchyma was observed. Minimal focal infiltration of mononuclear cells in the interstitial space between alveolar walls was noted. Normal histomorphological features of bronchi and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed.

**Group- G: Animal treated with ETH+ PAS+ Aloe vera juice:** In male rats, minimal focal congested vessels in the lung parenchyma. Focal infiltration of mononuclear cells in the interstitial space between alveolar walls was observed. Normal histomorphological features of bronchi and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed. In female rats, histomorphological features of bronchi and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed.

**Group-H: Animal treated with Aloe vera juice only:** In male rats, normal histomorphological features of bronchi and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed. In female rats, histomorphological features of bronchi and alveolar tissue with intact cellular details. Normal bronchiolar epithelium was observed.

**Photograph 1 (A- H): Showing Effect of Aloe vera Juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Lung of Male and Female Sprague-dawley rats**



	
<b>D- Male Animals treated with ETH + PAS 90 mg/kg</b>	<b>D- Female Animals treated with ETH + PAS 90 mg/kg</b>
	
<b>E- Male Animal treated with ETH+Aloe vera juice 90mg/kg</b>	<b>E- Female Animal treated with ETH+Aloe vera juice 90mg/kg</b>
	
<b>F- Male Animal treated with PAS +Aloe vera juice 90mg/kg</b>	<b>F- Female Animal treated with PAS +Aloe vera juice 90mg/kg</b>
	
<b>G- Male Animal treated with ETH+PAS+ Aloe vera juice 90mg/kg</b>	<b>G- Female Animal treated with ETH+PAS+ Aloe vera juice 90mg/kg</b>
	
<b>H- Male Animal treated with Only Aloe vera juice 90mg/kg</b>	<b>H- Female Animal treated with Only Aloe vera juice 90mg/kg</b>

Research<sup>12</sup> found that the rats treated with fluoride showed conjunction, thickened alveolar septa with infiltration of MNC and RBC's, the aggregation in the focal periveascular

and bronchiolar lymphoid, hyperplasia of bronchial epithelium of the lungs. Whereas in rats treated with *Aloe vera* extract in control and experimental group showed

normalization of the lungs. Their study was in agreement with the study carried out by <sup>13</sup>. These changes might be because of depletion of antioxidant defense system by fluoride which leads to oxidative stress to toxic fluoride intoxicated tissues <sup>14</sup>. In control and fluoride intoxicated treated group supplemented with *Aloe vera* groups, the corresponding toxin treated group ameliorated. This might be due to the antioxidant and anti-inflammatory properties of *Aloe vera* <sup>15</sup>.

In the present study, it was found that the Male and female rats treated with ETH and PAS showed, mild to minimal changes in lungs, whereas supplementations of *Aloe vera* juice independently or in combination with ETH and PAS shows ameliorated the histomorphological features of bronchi and alveolar tissue with intact cellular details of the normal bronchiolar epithelium. This may be due to *Aloe vera* juice has antioxidant and anti-inflammatory properties.

**Photograph 2 (A- H): Showing Effect of *Aloe vera* Juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Heart of Male and Female Sprague-dawley rats.**

**Group- A: NC (Normal Control):** In normal control male and female rats, normal histomorphological features of cardiac muscle fibers in the myocardium. Absence of inflammatory or pathological changes in heart tissue was noted. In normal control female rat, normal histomorphological features of cardiac muscle fibers in the myocardium. Absence of inflammatory or pathological changes in heart tissue was noted.

**Group- B: Animals treated with ETH:** In male and female rats, a normal histomorphological feature of cardiac muscle fibers in the myocardium was noted. Focal congested blood vascular tissue. Focal degenerative changes of cardiac fibers with deranged length of cardiac firers were observed.

**Group- C: Animals treated with PAS:** In male and female rats, a normal histomorphological feature of cardiac muscle fibers in the myocardium was noted. Focal congested blood vascular tissue. Focal degenerative changes of cardiac fibers with deranged length of cardiac firers were observed.

**Group- D: Animals treated with ETH + PAS:** In male and female rats, a normal histomorphological feature of cardiac muscle fibers in the myocardium was noted. Focal congested blood vascular tissue. Focal degenerative changes of cardiac fibers with deranged length of cardiac firers were observed.

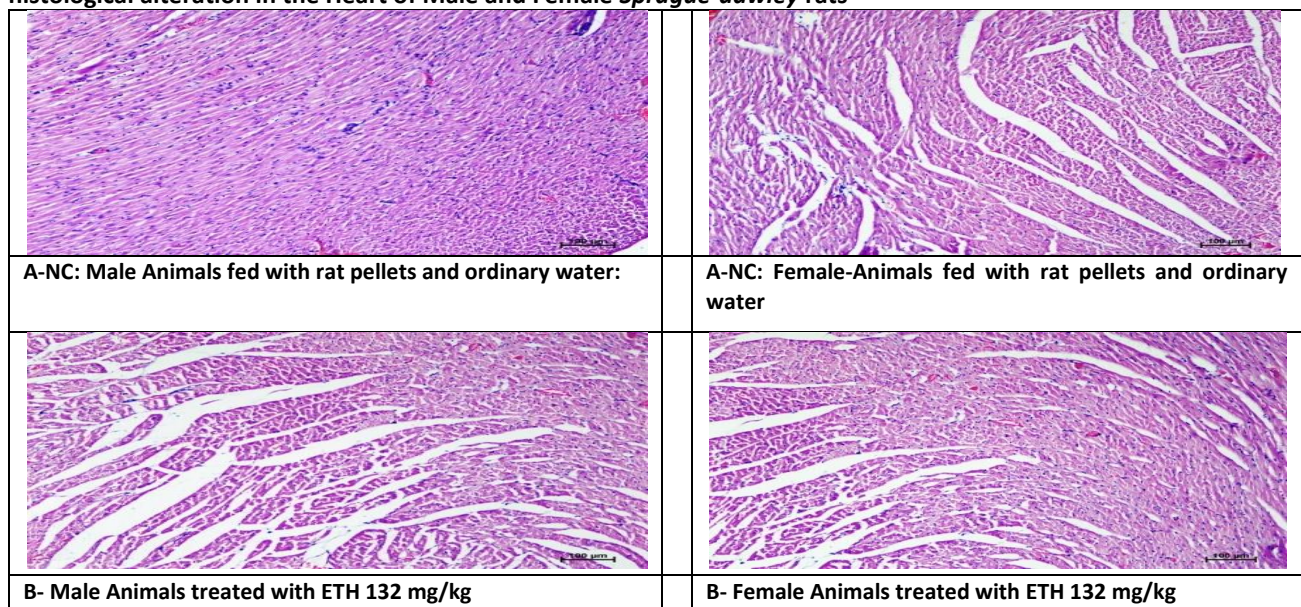
**Group- E: Animal treated with ETH+ *Aloe vera* juice:** In male and female rats, a normal histomorphological feature of cardiac muscle fibers in the myocardium was noted. Focal congested blood vascular tissue. Focal degenerative changes of cardiac fibers with deranged length of cardiac firers were observed.

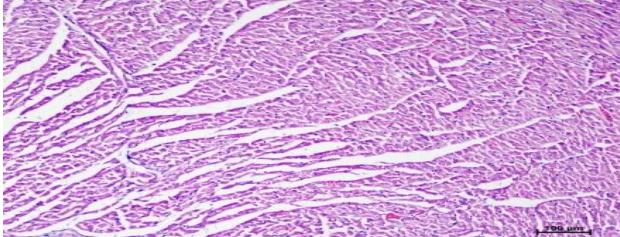
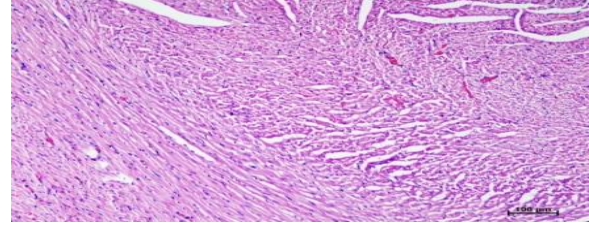
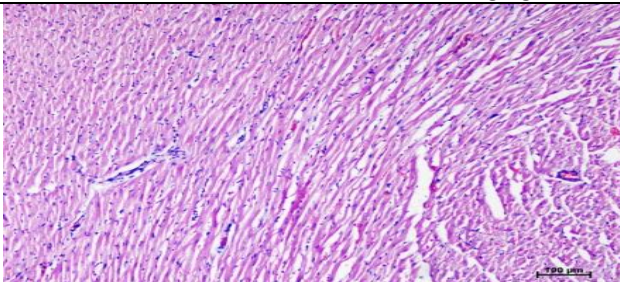
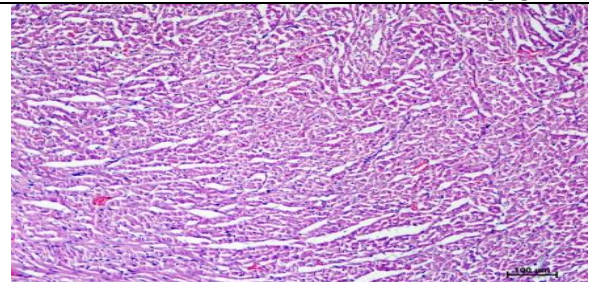
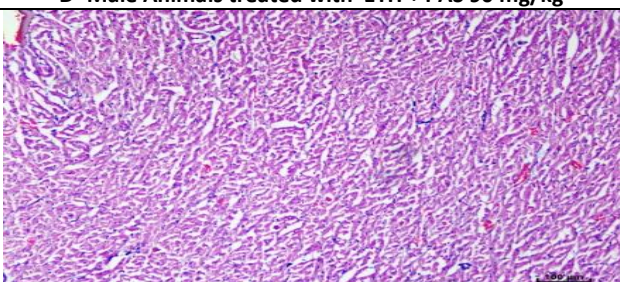
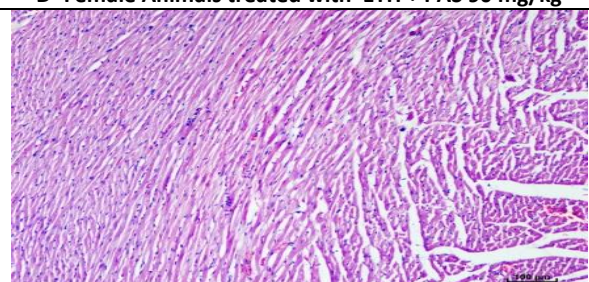
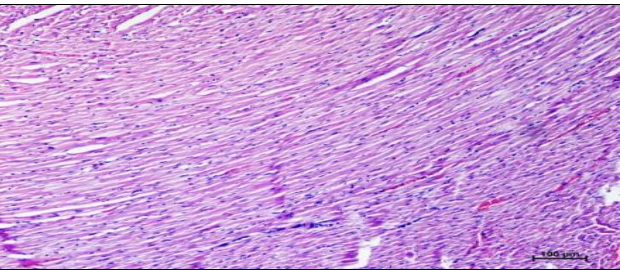
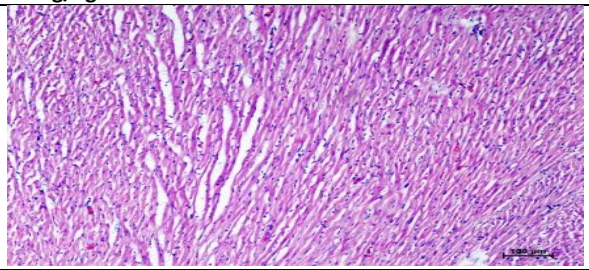
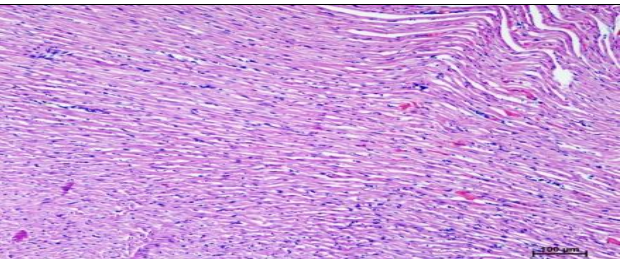
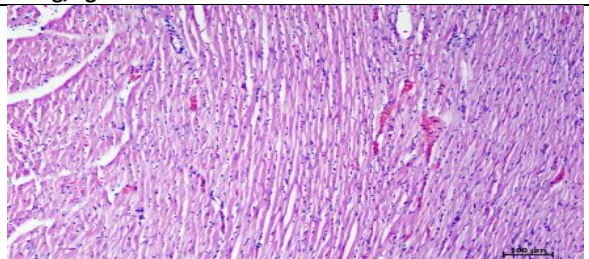
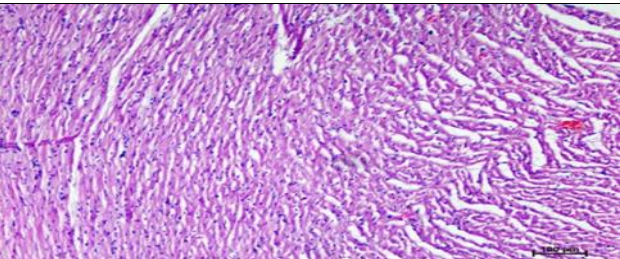
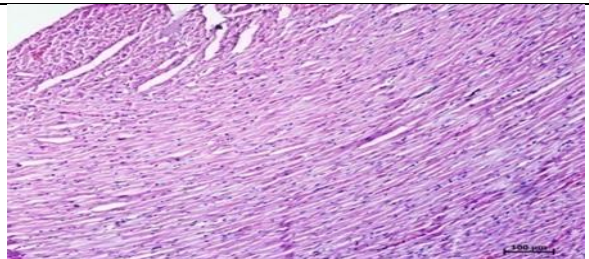
**Group- F: Animal treated with PAS +*Aloe vera* juice:** In male and female rats, a normal histomorphological feature of cardiac muscle fibers in the myocardium was noted. Focal congested blood vascular tissue. Focal degenerative changes of cardiac fibers with deranged length of cardiac firers were observed.

**Group- G: Animal treated with ETH+ PAS+ *Aloe vera* juice:** In male and female rats, a normal histomorphological feature of cardiac muscle fibers in the myocardium was noted. Focal congested blood vascular tissue. Focal degenerative changes of cardiac fibers with deranged length of cardiac firers were observed.

**Group-H: Animal treated with *Aloe vera* juice only:** In male and female rats, a normal histomorphological feature of cardiac muscle fibers in the myocardium was noted. Focal congested blood vascular tissue. Focal degenerative changes of cardiac fibers with deranged length of cardiac firers were observed.

**Photograph 2 (A- H): Showing Effect of *Aloe vera* Juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Heart of Male and Female Sprague-dawley rats**



	
<b>C- Male Animals treated with PAS 400mg/kg</b>	<b>C- Female Animals treated with PAS 400mg/kg</b>
	
<b>D- Male Animals treated with ETH + PAS 90 mg/kg</b>	<b>D- Female Animals treated with ETH + PAS 90 mg/kg</b>
	
<b>E- Male Animal treated with ETH+Aloe vera juice 90mg/kg</b>	<b>E-Female Animal treated with ETH+Aloe vera juice 90mg/kg</b>
	
<b>F- Male Animal treated with PAS +Aloe vera juice 90mg/kg</b>	<b>F-Female Animal treated with PAS +Aloe vera juice 90mg/kg</b>
	
<b>G-Male Animal treated with ETH+PAS+ Aloe vera juice 90mg/kg</b>	<b>G- Female Animal treated with ETH+PAS+ Aloe vera juice 90mg/kg</b>
	
<b>H- Male Animal treated with Only Aloe vera juice 90mg/kg</b>	<b>H- Female Animal treated with Only Aloe vera juice 90mg/kg</b>

In heart, mild MNC infiltration in between the cardiac muscle fibers, focal sarcolytic changes, mild proliferation of fibroblasts, small pockets of hemorrhages and thickened blood vessels were evident in most of the NaF treated rats. These changes might be due to the decreased antioxidant enzyme activity or due to membrane lipid peroxidation caused by fluoride. No reports were available in literature to compare lesions in heart due to NaF toxicity in rats. The changes noticed in the amelioration group were very mild when compared to group II which might be due to the radical scavenging activity of *Aloe vera*<sup>16</sup>. *Aloe vera* has been reported to stimulate the beta receptor cells of langendorff perfused isolated heart<sup>17</sup>. The study of<sup>18</sup> reported that the Aloe has antioxidant, free radical scavenging and cardio active property. Higher doses of *Aloe vera* in a prolonged period may cause OTc interval in albino rat, therefore administration of *Aloe vera* at higher dose in a prolonged period may be cardio toxic<sup>19</sup>.

In the present study, it was found the conjunction of cardiac muscle fibers in the myocardium and focal congested blood vascular tissue. Focal degenerative changes of cardiac fibers with deranged length of cardiac fibers were noted in rats treated with ETH and PAS, whereas rats treated with *Aloe vera* juice independently or in combination with ETH and PAS shows revert change in histomorphological features of cardiac muscle fibers in the myocardium and improvement in focal congested blood vascular tissue and improvement in the degenerative changes of cardiac fibers with deranged length of cardiac fibers were observed. This proves that *Aloe vera* has heart protective activity.

**Photograph 3 (A- H): Showing Effect of *Aloe vera* Juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Pancreas of Male and Female Sprague- dawley rats**

**Group- A: NC (Normal Control):** In normal male and female rats, normal histological features of exocrine and endocrine pancreatic tissue were observed. Endocrine pancreatic tissue showed adequate and normal cellular details of islands of langerhans with intact cellular details of beta cells. In normal female rat, normal histological features of exocrine and endocrine pancreatic tissue were observed. Endocrine pancreatic tissue showed adequate and normal cellular details of islands of langerhans with intact cellular details of beta cells.

**Group- B: Animals treated with ETH:** In male and female rats, normal histological features of exocrine and endocrine pancreatic tissue were observed. Endocrine pancreatic tissue showed adequate and normal cellular details of islands of langerhans with intact cellular details of beta cells.

**Group- C: Animals treated with PAS:** In male and female rats, normal histological features of exocrine and endocrine pancreatic tissue were observed. Endocrine pancreatic tissue showed adequate and normal cellular details of islands of langerhans with intact cellular details of beta cells.

**Group- D: Animals treated with ETH + PAS:** In male and female rats, normal histological features of exocrine and endocrine pancreatic tissue were observed. Endocrine pancreatic tissue showed adequate and normal cellular details of islands of langerhans with intact cellular details of beta cells.

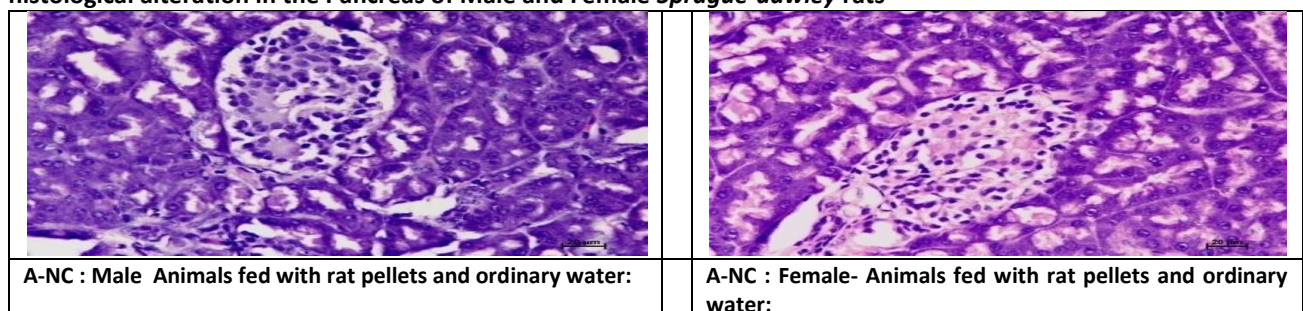
**Group- E: Animal treated with ETH+ *Aloe vera* juice:** In male and female rats, normal histological features of exocrine and endocrine pancreatic tissue were observed. Endocrine pancreatic tissue showed adequate and normal cellular details of islands of langerhans with intact cellular details of beta cells.

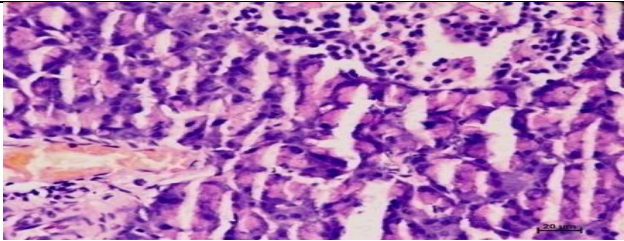
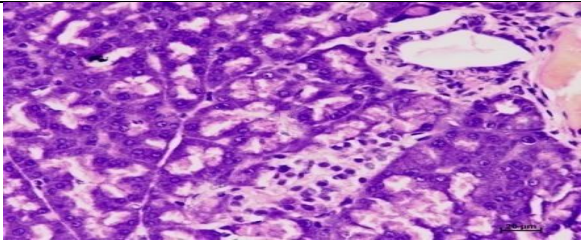
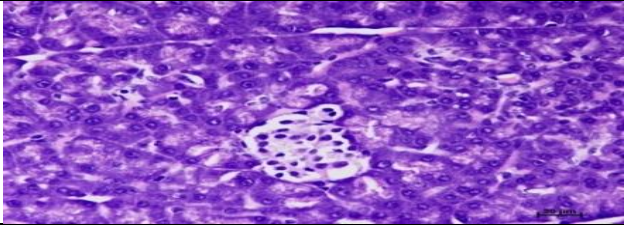
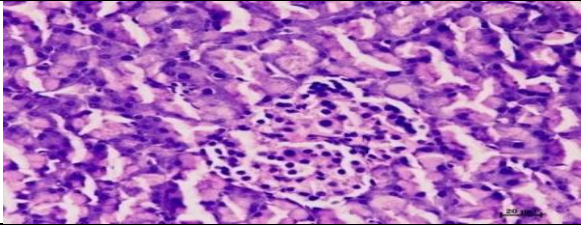
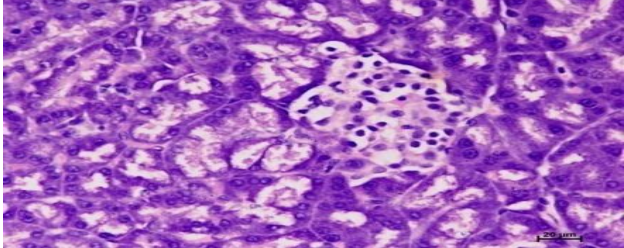
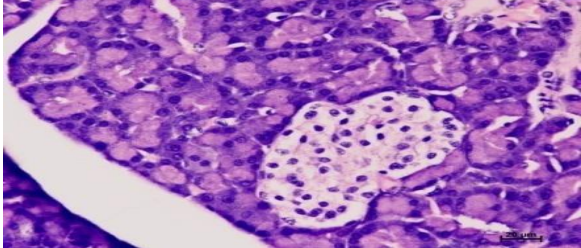
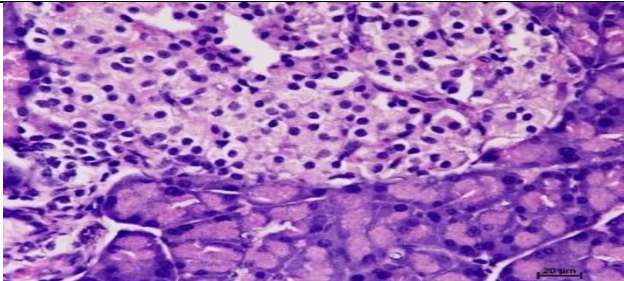
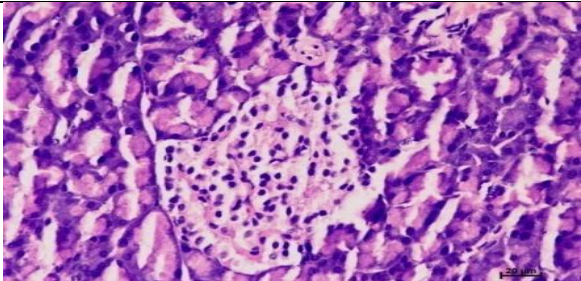
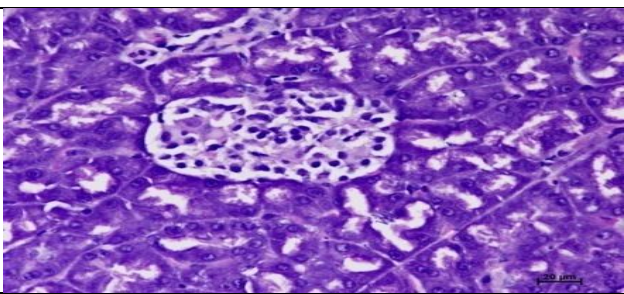
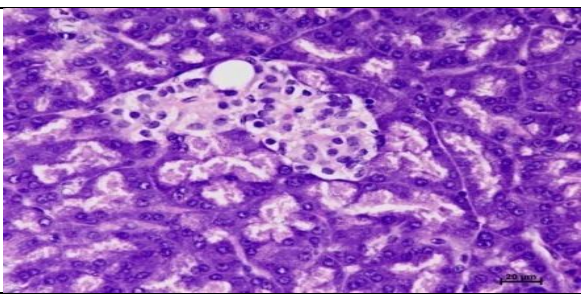
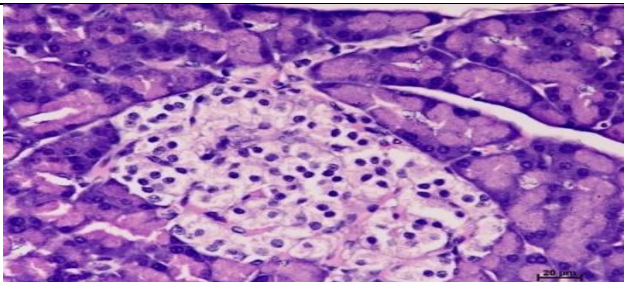
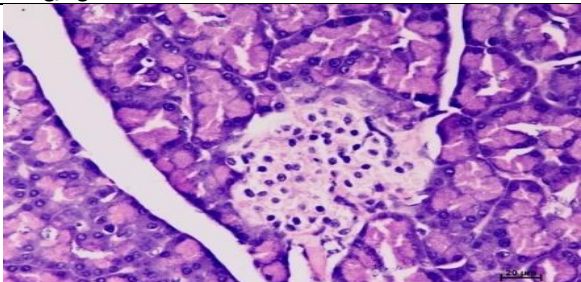
**Group- F: Animal treated with PAS +*Aloe vera* juice:** In male and female rats, normal histological features of exocrine and endocrine pancreatic tissue were observed. Endocrine pancreatic tissue showed adequate and normal cellular details of islands of langerhans with intact cellular details of beta cells.

**Group- G: Animal treated with ETH+ PAS+ *Aloe vera* juice:** In male and female rats, normal histological features of exocrine and endocrine pancreatic tissue were observed. Endocrine pancreatic tissue showed adequate and normal cellular details of islands of langerhans with intact cellular details of beta cells.

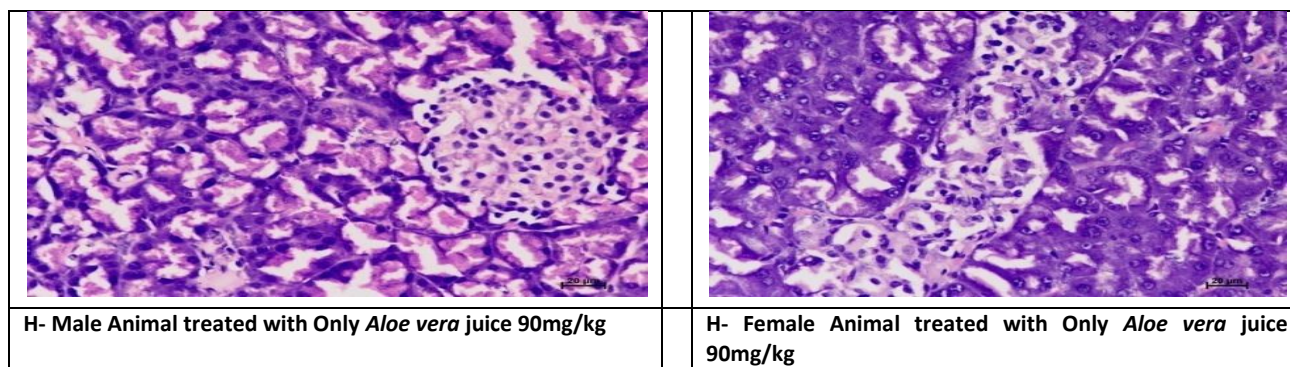
**Group-H: Animal treated with *Aloe vera* juice only:** In male and female rats, normal histological features of exocrine and endocrine pancreatic tissue were observed. Endocrine pancreatic tissue showed adequate and normal cellular details of islands of langerhans with intact cellular details of beta cells.

**Photograph 3 (A- H): Showing Effect of *Aloe vera* Juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Pancreas of Male and Female Sprague-dawley rats**



	
<b>B- Male Animals treated with ETH 132 mg/kg</b>	<b>B- Female Animals treated with ETH 132 mg/kg</b>
	
<b>C- Male Animals treated with PAS 400mg/kg</b>	<b>C- Female Animals treated with PAS 400mg/kg</b>
	
<b>D- Male Animals treated with ETH + PAS 90 mg/kg</b>	<b>D- Female Animals treated with ETH + PAS 90 mg/kg</b>
	
<b>E- Male Animal treated with ETH+Aloe vera juice 90mg/kg</b>	<b>E-Female Animal treated with ETH+Aloe vera juice 90mg/kg</b>
	
<b>F- Male Animal treated with PAS +Aloe vera juice 90mg/kg</b>	<b>F- Female Animal treated with PAS +Aloe vera juice 90mg/kg</b>
	
<b>G- Male Animal treated with ETH+PAS+ Aloe vera juice 90mg/kg</b>	<b>G- Female Animal treated with ETH+PAS+ Aloe vera juice 90mg/kg</b>





The STZ-induced diabetic rats showed progression in terms of quality and quantity by gaining the number, diameter, volume and area of the pancreatic islets when treated with *Aloe vera* extract as compared to the untreated diabetic rats<sup>20</sup>. Another study they showed amelioration effect in pancreas of rats treated with *Aloe vera* extract. *Aloe vera* extract brings back the FPG levels to normal in STZ-induced diabetic rats<sup>21</sup>. These observations were in agreement and supported<sup>22-23</sup> who found that the treatment of *Aloe vera* extract lowering the blood-glucose level and protect the pancreatic  $\beta$ -cells in STZ induced diabetic rats. This might be because of proliferation of pancreatic  $\beta$ -cells, by increasing the secretion of insulin and increasing the oxidative capacity<sup>24,25,26</sup>. The findings of<sup>27</sup> showed an increased serum insulin level could be the ability to synthesize the pancreatic  $\beta$ -cells and or regeneration of pancreatic  $\beta$ -cells due to *Aloe vera* treatment in STZ-induced diabetic rats. These findings are in the agreement with the study carried out by<sup>28</sup> and<sup>29</sup>. It has also been reported that, there are number of plant extracts showed anti-diabetic properties by showing the mechanisms like *Aloe vera* extract<sup>30,31,32,33</sup>. Some of the literature also showed that the constituents of *Aloe vera* have anti diabetic and other pharmacological activities<sup>34-38</sup>.

In our present study no abnormality was detected in the histological architecture of pancreas. Animal treated with tuberculosis drugs ETH and PAS, either in different combinations with or without *Aloe vera* juice or independently showed normal histological features of exocrine and endocrine pancreatic tissue. Endocrine pancreatic tissue showed adequate and normal cellular details of islets of langerhans with intact cellular details of beta cells.

**Photograph 4 (A- H): Showing Effect of *Aloe vera* Juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Spleen of Male and Female Sprague-dawley rats**

**Group- A: NC (Normal Control):** In male and female rats, normal histomorphological features of red pulp and white pulp was seen. Adequate lymphoid cellular populations in the lymphoid tissue were observed. Focal hemosiderosis was observed. Absence of pathological changes in the splenic tissue was noted.

**Group- B: Animals treated with ETH:** In male and female rats, normal histomorphological features of red pulp and white pulp was seen. Adequate lymphoid cellular populations in the lymphoid tissue were observed. Focal hemosiderosis was observed. Absence of pathological changes in the splenic tissue was noted.

**Group- C: Animals treated with PAS:** In male and female rats, normal histomorphological features of red pulp and white pulp was seen. Adequate lymphoid cellular populations in the lymphoid tissue were observed. Focal hemosiderosis was observed. Absence of pathological changes in the splenic tissue was noted.

**Group- D: Animals treated with ETH + PAS:** In male and female rats, normal histomorphological features of red pulp and white pulp was seen. Adequate lymphoid cellular populations in the lymphoid tissue were observed. Focal hemosiderosis was observed. Absence of pathological changes in the splenic tissue was noted.

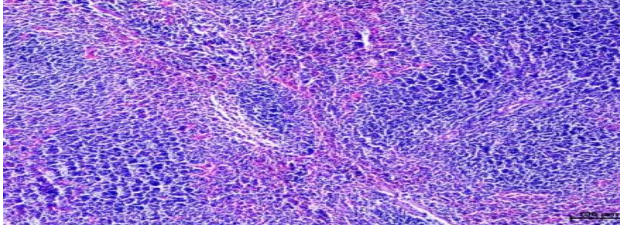
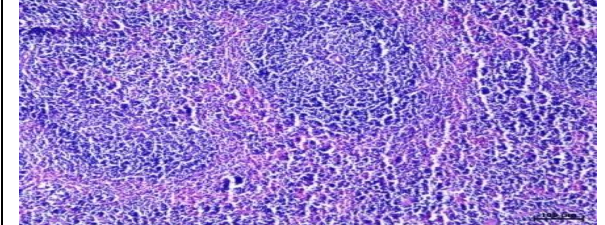
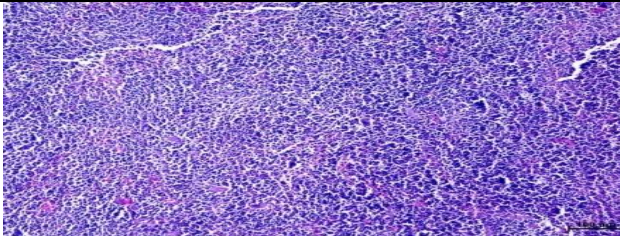
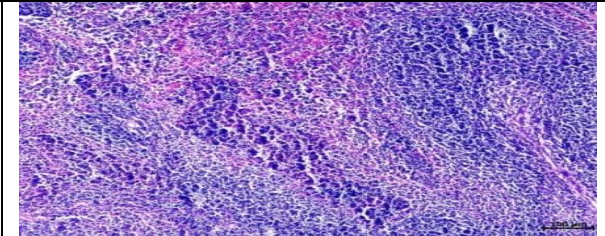
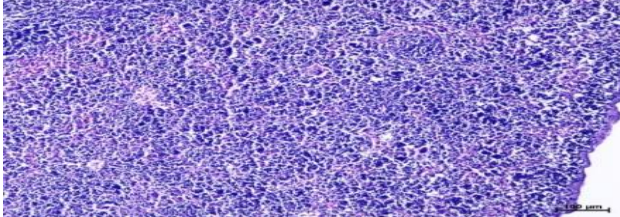
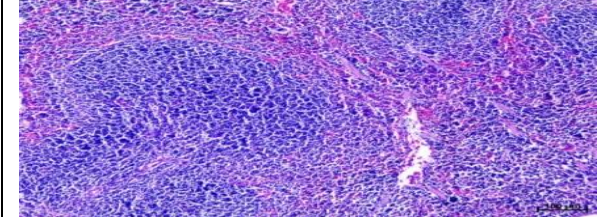
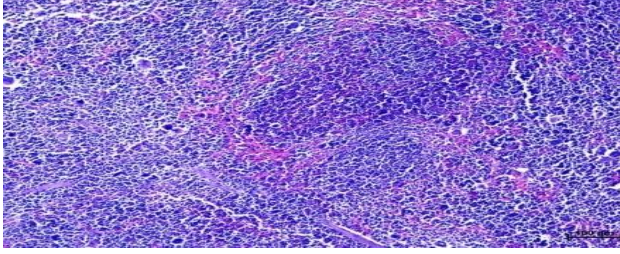
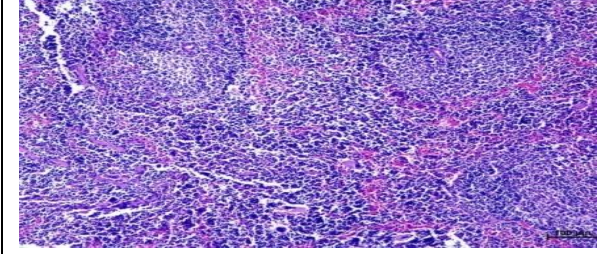
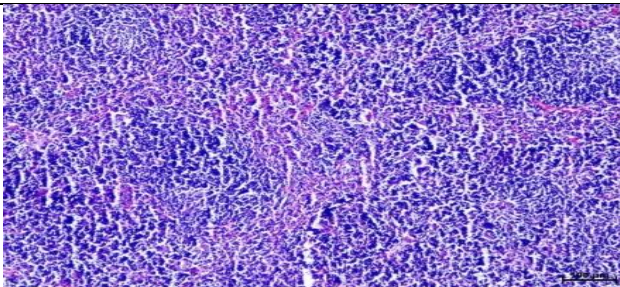
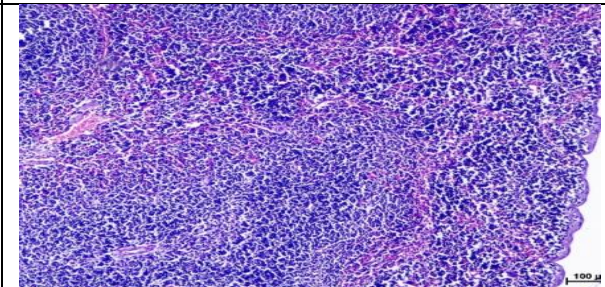
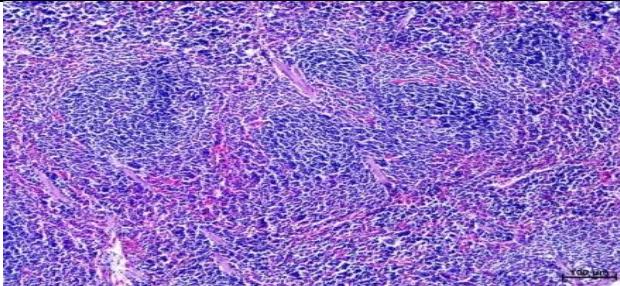
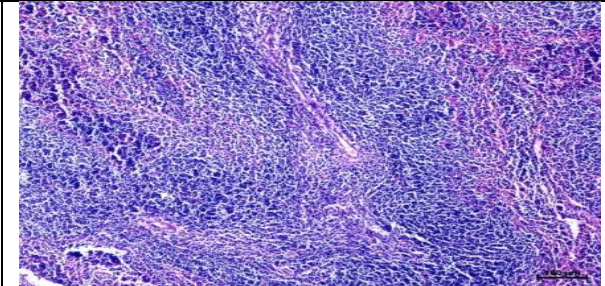
**Group- E: Animal treated with ETH+ *Aloe vera* juice:** In male and female rats, normal histomorphological features of red pulp and white pulp was seen. Adequate lymphoid cellular populations in the lymphoid tissue were observed. Focal hemosiderosis was observed. Absence of pathological changes in the splenic tissue was noted.

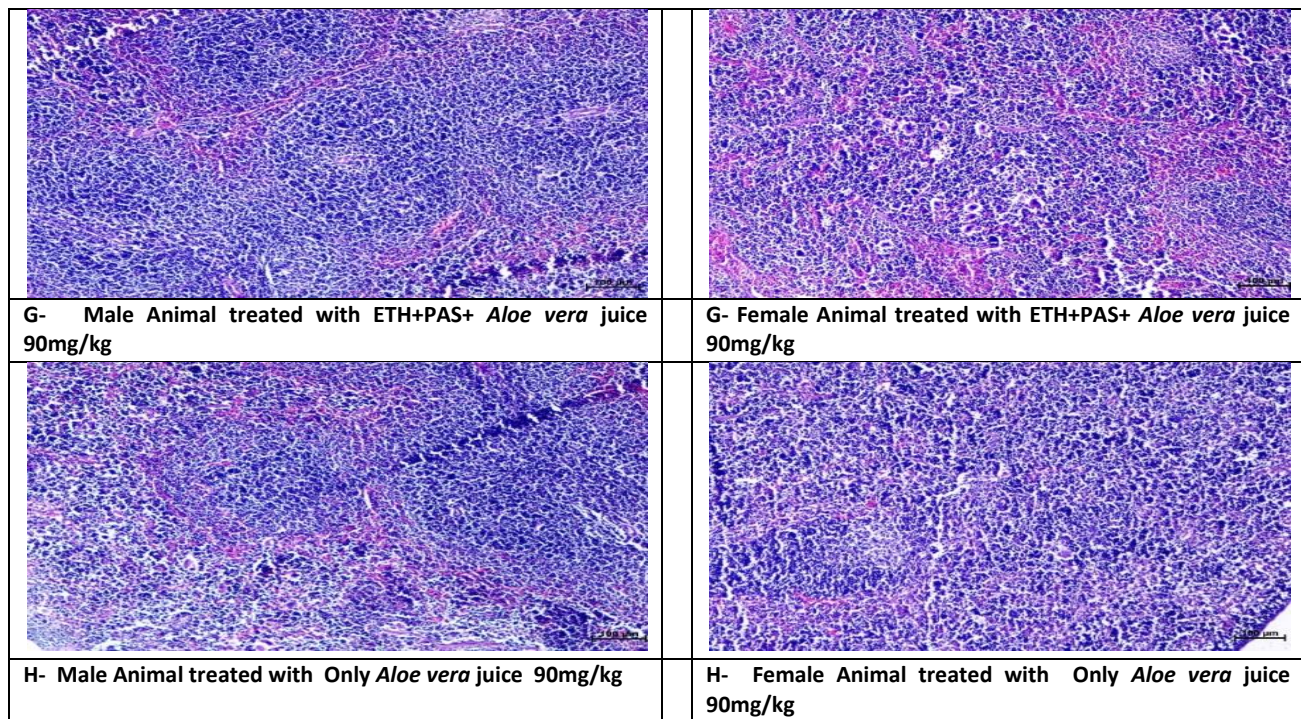
**Group- F: Animal treated with PAS +*Aloe vera* juice:** In male and female rats, normal histomorphological features of red pulp and white pulp was seen. Adequate lymphoid cellular populations in the lymphoid tissue were observed. Focal hemosiderosis was observed. Absence of pathological changes in the splenic tissue was noted.

**Group- G: Animal treated with ETH+ PAS+ *Aloe vera* juice:** In male and female rats, normal histomorphological features of red pulp and white pulp was seen. Adequate lymphoid cellular populations in the lymphoid tissue were observed. Focal hemosiderosis was observed. Absence of pathological changes in the splenic tissue was noted.

**Group-H: Animal treated with *Aloe vera* juice only:** In male and female rats, normal histomorphological features of red pulp and white pulp was seen. Adequate lymphoid cellular populations in the lymphoid tissue were observed. Focal hemosiderosis was observed. Absence of pathological changes in the splenic tissue was noted.

**Photograph 4 (A- H): Showing Effect of *Aloe vera* Juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Spleen of Male and Female *Sprague-dawley* rats**

	
A-NC: Male Animals fed with rat pellets and ordinary water:	A-NC: Female- Animals fed with rat pellets and ordinary water:
	
B- Male Animals treated with ETH 132 mg/kg	B- Female Animals treated with ETH 132 mg/kg
	
C- Male Animals treated with PAS 400mg/kg	C- Female Animals treated with PAS 400mg/kg
	
D- Male Animals treated with ETH + PAS 90 mg/kg	D- Female Animals treated with ETH + PAS 90 mg/kg
	
E- Male Animal treated with ETH+ <i>Aloe vera</i> juice 90mg/kg	E- Female Animal treated with ETH+ <i>Aloe vera</i> juice 90mg/kg
	
F- Male Animal treated with PAS + <i>Aloe vera</i> juice 90mg/kg	F- Female Animal treated with PAS + <i>Aloe vera</i> juice 90mg/kg



In the present study no abnormality was detected in the histological architecture of spleen. Animal treated with tuberculosis drugs ETH and PAS, either in different combinations with or without *Aloe vera* juice or independently showed normal histomorphological features of red pulp and white pulp. Adequate lymphoid cellular populations in the lymphoid tissue were observed. Focal hemosiderosis was observed. Absence of pathological changes in the splenic tissue was noted.

**Photograph 5 (A- H): Showing Effect of *Aloe vera* Juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Testis and Ovary of Male and Female *Sprague- dawley* rats**

**Group- A: NC (Normal Control):** In normal control male rats, normal and intact seminiferous tubules with spermatogenesis and sperm formation in lumen of tubules were observed. In normal control female rats, normal histomorphological features of ovarian tissue with presence of developing follicles and corpus luteum was seen. Congested vasculature of ovarian parenchyma was observed.

**Group- B: Animals treated with ETH:** In male rats, normal and intact seminiferous tubules with spermatogenesis and sperm formation in lumen of tubules were observed. In female rats, normal histomorphological features of ovarian tissue with presence of developing follicles and corpus luteum was seen. Congested vasculature of ovarian parenchyma was observed.

**Group- C: Animals treated with PAS:** In male rats, normal and intact seminiferous tubules with spermatogenesis and sperm formation in lumen of tubules were observed. In female rats, normal histomorphological features of ovarian tissue with presence of developing follicles and corpus

luteum was seen. Congested vasculature of ovarian parenchyma was observed.

**Group- D: Animals treated with ETH + PAS:** In male rats, normal and intact seminiferous tubules with spermatogenesis and sperm formation in lumen of tubules were observed. In normal control female rats, normal histomorphological features of ovarian tissue with presence of developing follicles and corpus luteum was seen. Congested vasculature of ovarian parenchyma was observed.

**Group- E: Animal treated with ETH+ *Aloe vera* juice:** In male rats, normal and intact seminiferous tubules with spermatogenesis and sperm formation in lumen of tubules were observed. In normal control female rats, normal histomorphological features of ovarian tissue with presence of developing follicles and corpus luteum was seen. Congested vasculature of ovarian parenchyma was observed.

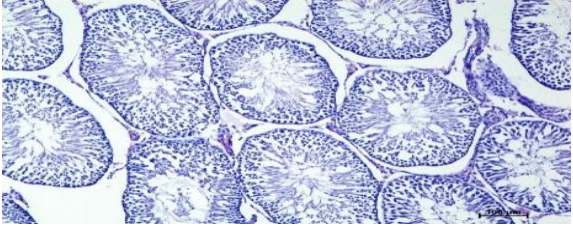
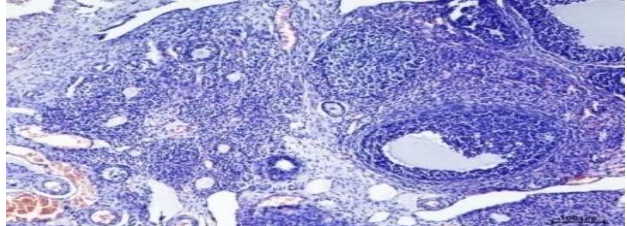
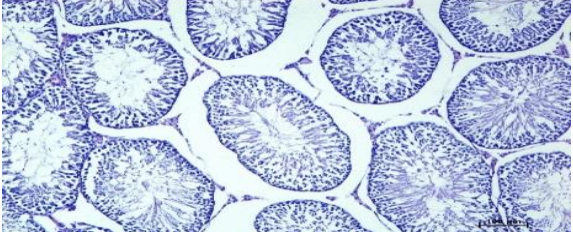
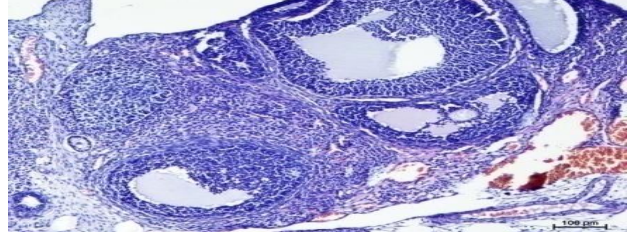
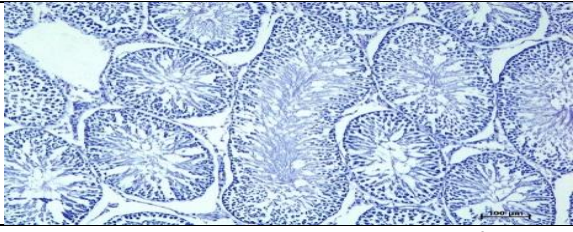
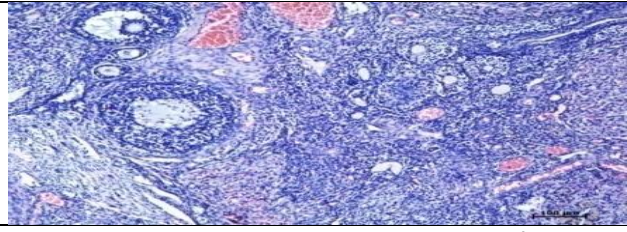
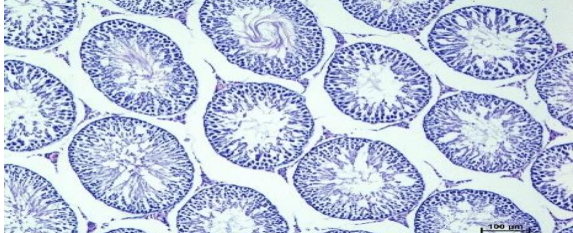
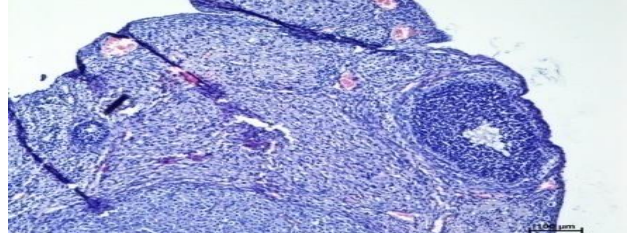
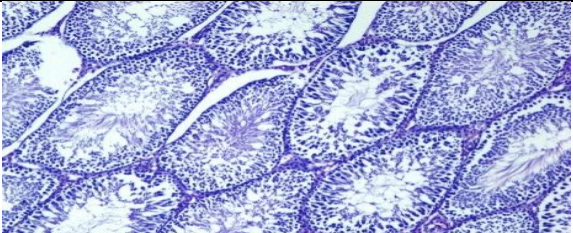
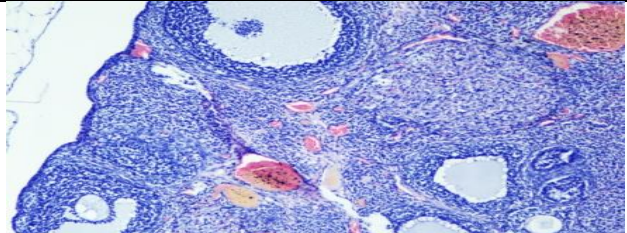
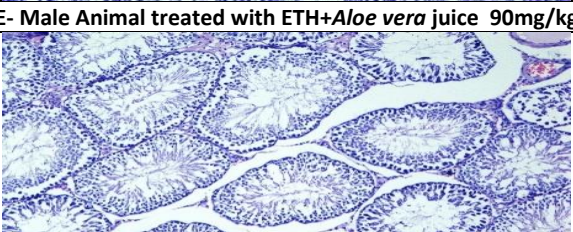
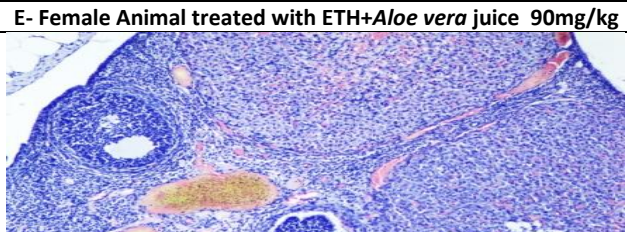
**Group- F: Animal treated with PAS +*Aloe vera* juice:** In male rats, normal and intact seminiferous tubules with spermatogenesis and sperm formation in lumen of tubules were observed. In female rats, normal histomorphological features of ovarian tissue with presence of developing follicles and corpus luteum was seen. Congested vasculature of ovarian parenchyma was observed.

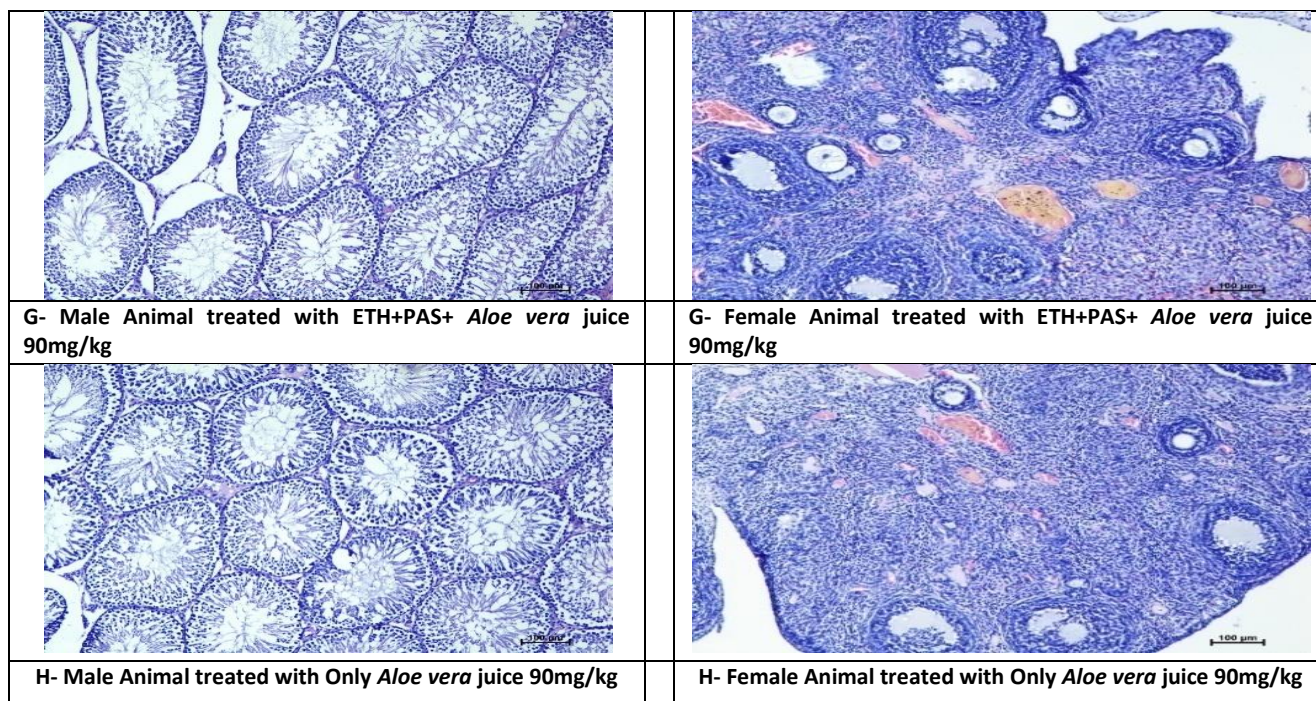
**Group- G: Animal treated with ETH+ PAS+ *Aloe vera* juice:** In male rats, normal and intact seminiferous tubules with spermatogenesis and sperm formation in lumen of tubules were observed. In female rats, normal histomorphological features of ovarian tissue with presence of developing follicles and corpus luteum was seen. Congested vasculature of ovarian parenchyma was observed.

**Group-H: Animal treated with *Aloe vera* juice only:** In male rats, normal and intact seminiferous tubules with spermatogenesis and sperm formation in lumen of tubules were observed. In female rats, normal histomorphological

features of ovarian tissue with presence of developing follicles and corpus luteum was seen. Congested vasculature of ovarian parenchyma was observed.

**Photograph 5 (A- H): Showing Effect of *Aloe vera* juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Testis and Ovary of *Sprague-dawley* rats**

	
<b>A-NC: Male-Animals fed with rat pellets and ordinary water:</b>	<b>A-NC: Female-Animals fed with rat pellets and ordinary water:</b>
	
<b>B- Male Animals treated with ETH 132 mg/kg</b>	<b>B- Female Animals treated with ETH 132 mg/kg</b>
	
<b>C- Male Animals treated with PAS 400mg/kg</b>	<b>C- Female Animals treated with PAS 400mg/kg</b>
	
<b>D- Male Animals treated with ETH + PAS 90 mg/kg</b>	<b>D- Female Animals treated with ETH + PAS 90 mg/kg</b>
	
<b>E- Male Animal treated with ETH+Aloe vera juice 90mg/kg</b>	<b>E- Female Animal treated with ETH+Aloe vera juice 90mg/kg</b>
	
<b>F- Male Animal treated with PAS +Aloe vera juice 90mg/kg</b>	<b>F- Female Animal treated with PAS +Aloe vera juice 90mg/kg</b>



The study carried out by <sup>39</sup> found the weight loss and affecting the metabolic rate in BPA –treated group. Their results are similar to <sup>40</sup>. The study carried out by <sup>41</sup> found that toxic stress can cause decrease in the testosterone level by lowering the antioxidant capacity and blocking the P450 cytochrome. This decreased in the testosterone may induce weight loss and decrease the metabolic rate in rats treated with BPA. When *Aloe vera* supplemented in BPA treated groups can decrease the toxic effect of BPA. This might be due to *Aloe vera* has antioxidant properties<sup>42, 43</sup>. The diameter of seminiferous tubules and thickness of epithelium were found reduced in the rats treated with BPA. This might be due to the production of low level of serum testosterone level and decreased in the weight of testis due to BPA toxicity <sup>44</sup>. Reduction in the weight of reproductive organs, reduction in the number of primary spermatocytes, spermatids and spermatogonia may be due to lowering the production of testosterone and affect the level of hormone due to BPA –treated rats, which leads to failure of spermatogenesis <sup>45</sup>. Their resent results are in consistent with the results of <sup>46, 47</sup>. Some studies showed non-significant difference in the body weight and the relative weight of the testis <sup>48</sup>, whereas others indicated the significant changes in body weight and relative organs weight <sup>49</sup>. These changes may be due to the difference in the doses, rout of administration, exposure time interval, nature of food, sex and strain of rats<sup>50</sup>. All these histopathological change studied and mentioned above showed toxicity due to BPA. When *Aloe vera* co-administered with BPA, showed ameliorated in the reproductive organs. This may be because of the flavonoids present in *Aloe vera* extract being able to increase the production of testosterone and antioxidant compounds present in it. It was also found that *Aloe vera* extract contains vitamin E is responsible for the reduction in the

number of Leydig and Sertoli cells. Vitamin E also improves the weight of testis, diameter of seminiferous tubules, and thickness of the germinal epithelium <sup>51</sup>.The study carried out by <sup>52</sup> found that the tramadol has harmful effect on reproductive organs of rats. Whereas the rats co-administered with *Aloe vera* accelerates healing of testicular structure and has positive effect on the level of testosterone.

In the present study no abnormality was detected in the histological architecture of testis and ovary. Animal treated with tuberculosis drugs ETH and PAS, either in different combinations with or without *Aloe vera* juice or independently showed normal histomorphological features. In male rats, normal and intact seminiferous tubules with spermatogenesis and sperm formation in lumen of tubules were observed. In female rats, normal histomorphological features of ovarian tissue with presence of developing follicles and corpus luteum was seen. Congested vasculature of ovarian parenchyma was observed.

**Photograph 6 (A- H): Showing Effect of *Aloe vera* Juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Brain of *Sprague-Dawley* rats.**

**Group- A: NC (Normal Control):** In normal control male and female rats, normal histomorphology of neuronal tissue and supporting tissue matrix in the brain cerebrum and cerebellum was seen. Absence of inflammatory / pathological changes in the brain tissue was noted.

**Group- B: Animals treated with ETH:** In male and female rats, normal histomorphology of neuronal tissue and supporting tissue matrix in the brain cerebrum and cerebellum was seen. Absence of inflammatory / pathological changes in the brain tissue was noted.

**Group- C: Animals treated with PAS:** In male and female rats, normal histomorphology of neuronal tissue and supporting tissue matrix in the brain cerebrum and cerebellum was seen. Absence of inflammatory / pathological changes in the brain tissue was noted.

**Group- D: Animals treated with ETH + PAS:** In male and female rats, normal histomorphology of neuronal tissue and supporting tissue matrix in the brain cerebrum and cerebellum was seen. Absence of inflammatory / pathological changes in the brain tissue was noted.

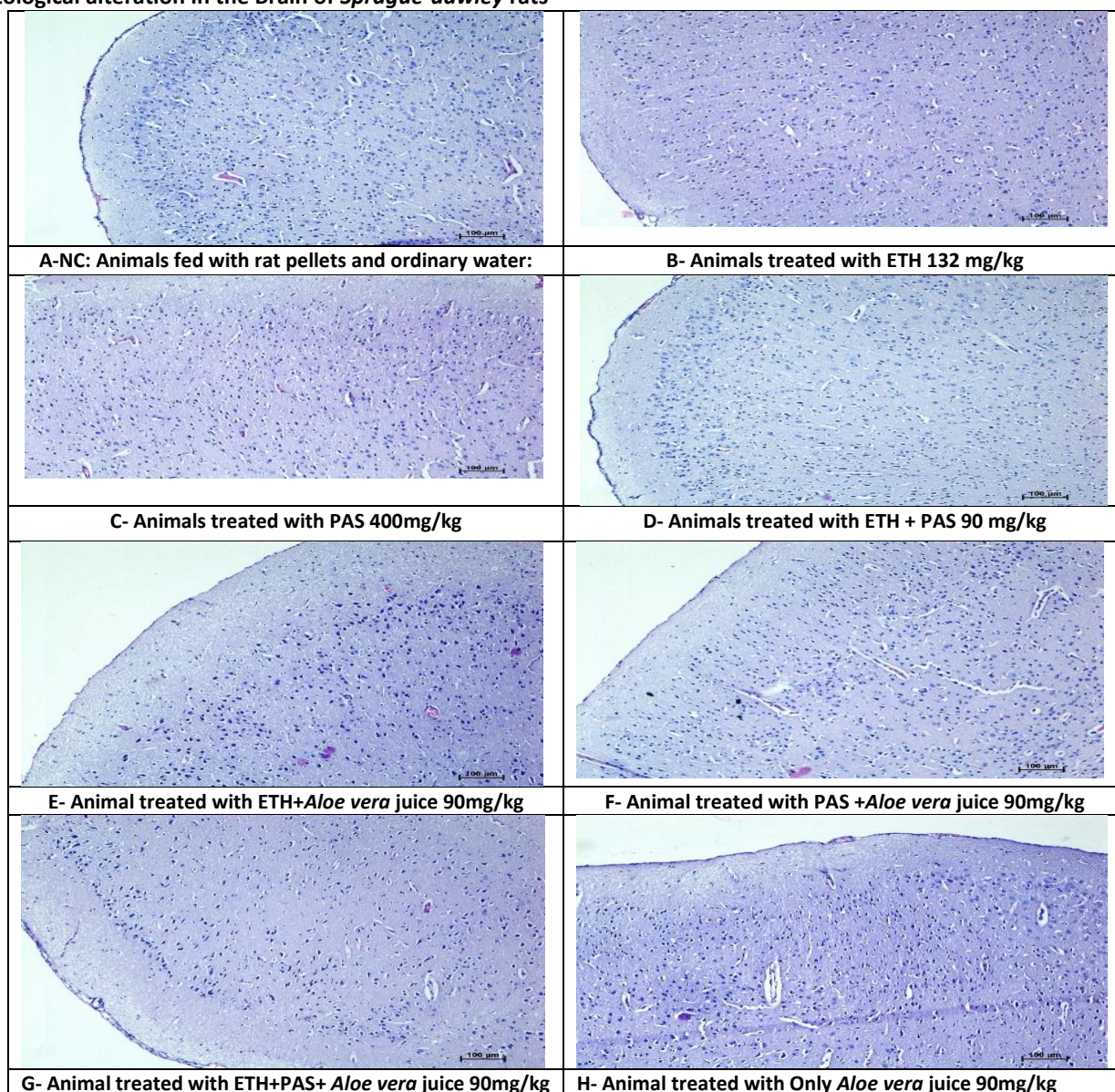
**Group- E: Animal treated with ETH+ Aloe vera juice:** In male and female rats, normal histomorphology of neuronal tissue and supporting tissue matrix in the brain cerebrum and cerebellum was seen. Absence of inflammatory / pathological changes in the brain tissue was noted.

**Group- F: Animal treated with PAS +Aloe vera juice:** In male and female rats, normal histomorphology of neuronal tissue and supporting tissue matrix in the brain cerebrum and cerebellum was seen. Absence of inflammatory / pathological changes in the brain tissue was noted.

**Group- G: Animal treated with ETH+ PAS+ Aloe vera juice:** In male and female rats, normal histomorphology of neuronal tissue and supporting tissue matrix in the brain cerebrum and cerebellum was seen. Absence of inflammatory / pathological changes in the brain tissue was noted.

**Group-H: Animal treated with Aloe vera juice only:** In male and female rats, normal histomorphology of neuronal tissue and supporting tissue matrix in the brain cerebrum and cerebellum was seen. Absence of inflammatory / pathological changes in the brain tissue was noted.

**Photograph 6 (A- H): Showing Effect of Aloe vera Juice and drugs Ethionamide and Para amino salicylic acid, on the histological alteration in the Brain of Sprague-dawley rats**



The study carried out by,<sup>53</sup> showed the ameliorated effect of *Aloe vera* extract in rat brain on toxicity induced by malathion. They found the pretreatment of *Aloe vera* ameliorated the toxic effect of malathion and also protected AChE activity from the malathion in rats brain. It was found and no any studies reported that the *Aloe vera* extract has no effect on brain edema after gastric ulcer<sup>54</sup>. There are some studies which pointing out that *Aloe vera* have anti-inflammatory effect which reduced the expression of inflammatory cytokines, like IL-1 $\beta$  and TNF- $\alpha$  and is responsible to decrease the Traumatic Brain Injury (TBI) in rats treated with *Aloe vera* extract<sup>55</sup>. The neuroprotective role of *Aloe vera* could be attributed to increased levels of pro inflammatory cytokines of brain like IL-1 $\beta$ , IL-6, TNF- $\alpha$  and TGF- $\beta$  after TBI were reduced by *Aloe vera* extract which suggest the protective potential of *Aloe vera* against TBI<sup>56</sup>. In the study<sup>57</sup> suggest that the malathion treated group showed the degeneration in the kidney, heart and focal gliosis and neuronal degeneration in the brain tissues. But after the treatment of *Aloe vera* extract to normal control and treat group ameliorated the toxicities of livers, kidneys, hearts, and brains in the rats. It was found that the dimethoate, an OP compound caused lymphocytic infiltration resulting in chronic, mild meningeal changes in the brain<sup>58</sup>. The study carried out by<sup>59</sup> found that the rats treated with fluoride showed neurotoxicity. This might be because of crossing blood brain barrier or by interfering the free radical generation or by affecting neural production by the fluoride. Their study supported by<sup>60</sup> suggesting that the mitochondrial electron transport enzymes or suppression of antioxidant enzymes in the brain cause Traumatic Brain Injury (TBI) when rats treated with fluoride. The study carried out by<sup>61</sup> noted the effect of *Aloe vera* on the toxicity induced by fluoride in brain, noted the amelioration mitochondrial electron transport enzymes or suppression of antioxidant enzymes in the brain. This might be due to the antioxidant property and free scavenging property of *Aloe vera*.

In the present study no abnormality was detected in the histological architecture of brain. Animal treated with tuberculosis drugs ETH and PAS, either in different combinations with or without *Aloe vera* juice or independently showed normal histomorphological features. In male and female rats, normal histomorphology of neuronal tissue and supporting tissue matrix in the brain cerebrum and cerebellum was seen. Absence of inflammatory / pathological changes in the brain tissue was noted.

## CONCLUSION

From the above results, it was found that the anti-tuberculosis drugs ETH and PAS induced toxicity in male and female *Sprague-dawley* rats by disturbing the histological structure from minimal to mild changes in the histoarchitecture of lungs, Heart and Kidneys of male and female *Sprague-dawley* either independently or in combination. It was also found that when the anti-tuberculosis drugs ETH and PAS co- administered with *Aloe*

*vera* juice found amelioration of the histoarchitecture of lungs, Heart and Kidneys of male and female *Sprague-dawley* to normal. This might be due to the antioxidant, anti-inflammatory and free scavenging property of *Aloe vera* juice. In our present study it was also found that, the rats treated with ETH and PAS drugs independently or in combination with *Aloe vera* juice, no histoarchitectural changes were observed in Brain, Pancreas, Spleen, testes, and ovaries of rat. This might be due to non-activation and non - infiltration of the drugs ETH and PAS on the membranes of the brain, pancreas, spleen, testes, and ovaries male and female *Sprague-dawley* rats. Thus, it confirms the antioxidant, anti-inflammatory and free scavenging property of *Aloe vera* juice to protect the histological structures of the different organs and glands of *Sprague-dawley* rat.

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## REFERENCES

1. WHO Global Tuberculosis Report, 2015
2. Bastian; R Colebunders, Treatment and prevention of multidrug-resistant tuberculosis. *Drugs*, 1999;58:633–661.
3. Lehmann, J. Para-Amino salicylic acid in the treatment of tuberculosis. *Dis Chest*. 1946;16(6):23-29.
4. Mitnick Carole., Jaime Bayona., Eda Palacios., Shin Sonya., Furin Jennifer., Felix Alcantara. et al. Community-based therapy for multidrug-resistant tuberculosis in Lima, Peru. *Engl. J* 2003; 348:119–128.
5. Yee D, Valiquette C, Pelletier M, Parisien I, Rocher I, Menzies D. Incidence of serious side effects from first-line antituberculosis drugs among patients treated for active tuberculosis. *Am J Respir Crit Care Med*. 2003; 167, 1472-7.
6. Ogbera, A.O.; Dada, O.; Adeyeye, F. and Jewo, P.I. Complementary and alternative medicine use in diabetes mellitus. *West Afr. J. Med*. 2010; 29(3): 158-162.
7. Grindlay D, Reynolds T. The *Aloe vera* phenomenon: a review of the properties and modern uses of the leaf parenchyma gel. *J. Ethnopharmacol*. 1986;16(2-3):117-51.
8. Nirmal Pugh, Samir A. Ross, Mahmoud A. Elsohly, and David S Pasco. Characterization of Aloeride, a New High-Molecular weight polysaccharide from *Aloe vera* with potent Immunostimulatory activity. *J. Agric. Food Chem*. 2001;49:1030-1034
9. Josias H. Hamman. Composition and Application of *Aloe vera* Leaf gel. *Molecules*. 2008;1599-1616.



10. Josias H. Hamman. (2008) Composition and Application of *Aloe vera* Leaf gel. *Molecules*. 1599- 1616.
11. Davidson CS. Guidelines for detection of hepatotoxicity due to drugs and chemicals. NIH publication, U.S.Department of Health and Education and Welfare NIH U.S.A. 1979.
12. Saritha V, Anil kumar KR, Khanum F Antioxidant and antibacterial activity of *Aloe vera* gel extracts. *Int J Pharmaceutical Bio Arch* .2010; 4: 376-384.
13. Ncu, Gulle K, Karaoz E, Gultekin F, Karaoz S, et al. Biochemical and histopathological effects of chronic fluorosis on lung tissues of first generation rats. *Biotechnol and Biotechnol Eq*. 2004.
14. Shivarajashankara YM, Shivashankara AR, Gopalakrishna Bhat P, Muddanna Rao S, Hanumanth Rao S. Histological changes in the brain of young fluoride intoxicated rats. *Fluoride*. 2002;35:12-21.
15. Sharrif Moghaddasi M, Sandeep Kumar Verma. *Aloe vera* their chemicals composition and applications: A review. *Int J Biol Med Res*. 2011; 2: 466-471.
16. Shibata T, Watanabe M, Tanaka K, Wada K, Inoue Y. Dynamic changes in expression of glutamate transporter mRNAs in developing brain. *Neuroreport*. 1996; 7: 705-709.
17. Kumar S, Singh BK, Pandey AK, Kumar A, Sharma SK, Raj HG, et al. A chromone analog inhibits TNF- $\alpha$  induced expression of cell adhesion molecules on human endothelial cells via blocking NF- $\kappa$ B activation. *Bioorg Med Chem*. 2007; 15: 2952- 2962.
18. Rajasekaran S, sivangnanam K, Subramanian S. Antioxidant effect of aloe of *Aloe vera* gel extract in streptozotocin-induced diabetes in rat. *Pharmacol. Rep*. 2005; 57: 90-96
19. Kumar Pradeep , Verma Sadhana , Singh Shraddha, Tiwari Sunita and Khan M. Y. Effect of *Aloe vera* (*Aloe barbadensis*) gel extract on repolarization state of myocardium in albino rat. *African Journal of Pharmacy and Pharmacology*. 2010; 4(12) : 885-889,
20. Noor Ayesha, Gunasekaran S. Vijayalakshmi M. A. Improvement of Insulin Secretion and Pancreatic  $\beta$ -cell Function in Streptozotocin-induced Diabetic Rats Treated with *Aloe vera* Extract. *Pharmacognosy Research*. 2017;9(1): 99-104.
21. Noor A, Gunasekaran S, Manickam AS, Vijayalakshmi MA. Antidiabetic activity of *Aloe vera* and histology of organs in streptozotocin induced diabetic rats. *Curr Sci* 2008; 94:1070-6.
22. Okyar A, Can A, Akev N, Baktir G, Sütülpinar N. Effect of *Aloe vera* leaves on blood glucose level in type I and type II diabetic rat models. *Phytother Res*. 2001; 15:157-61.
23. Eamlamnam K, Patumraj S, Visedopas N, Thong-Ngam D. Effects of *Aloe vera* and sucralfate on gastric microcirculatory changes, cytokine levels and gastric ulcer healing in rats. *World J Gastroenterol*. 2006; 12:2034-2039.
24. Shanmugasundaram ER, Gopinath KL, Radha Shanmugasundaram K, Rajendran VM. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given *Gymnema sylvestre* leaf extracts. *J Ethnopharmacol*. 1990; 30: 265-79.
25. Ashwini S, Bobby Z, Joseph M, Jacob SE, Padmapriya R. Insulin plant (*Costus pictus*) extract improves insulin sensitivity and ameliorates atherogenic dyslipidaemia in fructose induced insulin resistant rats: Molecular mechanism. *J Funct Foods*. 2015; 17:749-60.
26. Verma PR, Itankar PR, Arora SK. Evaluation of antidiabetic antihyperlipidemic and pancreatic regeneration, potential of aerial parts of *Clitoria ternatea*. *Rev Bras Farmacogn*. 2013; 23:819-29.
27. Hafizur RM, Kabir N, Chishti S. *Asparagus officinalis* extract controls blood glucose by improving insulin secretion and  $\beta$ -cell function in streptozotocin-induced type 2 diabetic rats. *Br J Nutr*. 2012; 108:1586-95.
28. Adeyemi DO, Komolafe OA, Adewole OS, Obuotor EM, Abiodun AA, Adenowo TK, et al. Histomorphological and morphometric studies of the pancreatic islet cells of diabetic rats treated with extracts of *Annona muricata*. *Folia Morphol (Warsz)*. 2010; 69:92-100.
29. Ramadan BK, Schaaln MF, Tolba AM. Hypoglycemic and pancreatic protective effects of *Portulaca oleracea* extract in alloxan induced diabetic rats. *BMC Complement Altern Med* 2017; 17:37.
30. Adeyemi DO, Komolafe OA, Adewole OS, Obuotor EM, Abiodun AA, Adenowo TK, et al. Histomorphological and morphometric studies of the pancreatic islet cells of diabetic rats treated with extracts of *Annona muricata*. *Folia Morphol (Warsz)*. 2010; 69:92-100.
31. Shanmugasundaram ER, Gopinath KL, Radha Shanmugasundaram K, Rajendran VM. Possible regeneration of the islets of Langerhans in streptozotocin-diabetic rats given *Gymnema sylvestre* leaf extracts. *J Ethnopharmacol*. 1990; 30: 265-79.
32. Hafizur RM, Kabir N, Chishti S. *Asparagus officinalis* extract controls blood glucose by improving insulin secretion and  $\beta$ -cell function in streptozotocin-induced type 2 diabetic rats. *Br J Nutr*. 2012; 108:1586-95.
33. Collombat P, Xu X, Heimberg H, Mansouri A. Pancreatic beta-cells: From generation to regeneration. *Semin Cell Dev Biol*. 2010; 21:838-44.
34. Hamman JH. Composition and applications of *Aloe vera* leaf gel. *Molecules* 2008; 13:1599-616.
35. Tanaka M, Misawa E, Ito Y, Habara N, Nomaguchi K, Yamada M, et al. Identification of five phytosterols from *Aloe vera* gel as anti-diabetic compounds. *Biol Pharm Bull* 2006; 29:1418-22.
36. Yagi A, Hegazy S, Kabbash A, Wahab EA. Possible hypoglycemic effect of *Aloe vera* L. High molecular weight fractions on type 2 diabetic patients. *Saudi Pharm J*. 2009; 17:209-15.
37. Huseini HF, Kianbakht S, Hajiaghah R, Dabaghian FH. Anti-hyperglycemic and anti-hypercholesterolemic effects of *Aloe vera* leaf gel in hyperlipidemic type 2 diabetic patients: A randomized double-blind placebo-controlled clinical trial. *Planta Med* 2012; 78:311-6.
38. Yimam M, Zhao J, Corneliusen B, Pantier M, Brownell L, Jia Q, et al. Blood glucose lowering activity of aloe based composition, UP780, in alloxan induced insulin dependent mouse diabetes model. *Diabetol Metab Syndr* 2014;6:61
39. Yousaf B, Amina, Liu G, Wang R, Qadir A, Ali MU, et al. Bisphenol A exposure and healing effects of *Adiantum capillus-veneris* L. plant extract (APE) in bisphenol A-induced reproductive toxicity in albino rats. *Environ Sci Pollut Res Int*. 2016; 23(12): 11645-11657.
40. Isidori AM, Giannetta E, Greco EA, Gianfrilli D, Bonifacio V, Isidori A. et al. Effects of testosterone on body composition, bone metabolism and serum lipid profile in middle-aged men: a meta-analysis. *Clin Endocrinol (Oxf)*. 2005; 63(3): 280-293.
41. Akingbemi BT, Sottas CM, Koulova AI, Klinefelter GR, Hardy MP. Inhibition of testicular steroidogenesis by the xenoestrogen bisphenol A is associated with reduced pituitary luteinizing hormone secretion and decreased steroidogenic enzyme gene expression in rat Leydig cells. *Endocrinology*. 2004; 145(2): 592-603.
42. Gaikwad K, Dhande S, Joshi YM, Kadam V. Protective effect of *Adiantum capillus* against chemically induced oxidative stress by cisplatin. *J Appli Pharm Sci*. 2013; 3(2): 65-68.
43. Akingbemi BT, Sottas CM, Koulova AI, Klinefelter GR, Hardy MP. Inhibition of testicular steroidogenesis by the xenoestrogen bisphenol A is associated with reduced pituitary luteinizing hormone secretion and decreased steroidogenic enzyme gene expression in rat Leydig cells. *Endocrinology*. 2004; 145(2): 592-603.
44. Jin P, Wang X, Chang F, Bai Y, Li Y, Zhou R, et al. Low dose bisphenol A impairs spermatogenesis by suppressing reproductive hormone production and promoting germ cell apoptosis in adult rats. *J Biomed Res*. 2013; 27(2): 135-144.





45. Mourad IM, Khadrawy YA. The sensitivity of liver, kidney and testis of rats to oxidative stress induced by different doses of bisphenol A. *Life Science*. 2012; 2(2): 19-28.
46. Mohamad Norazit A, Razak J, Abdulla SA, Azmil MA, Mohd A. Effects of soya bean extract, bisphenol A and 17 $\beta$ -estradiol on the testis and circulating levels of testosterone and estradiol among peripubertal juvenile male sprague-dawley rats. *Sains Malays*. 2012; 41(1): 63-69.
47. Rao Chitra K., Mathur KR. Effect of bisphenol A and co-administration of bisphenol A and vitamin C on epididymis of adult rats: a histological and biochemical study. *Asian J Androl*. 2003; 5(3): 203-208.
48. Aydogan M, Korkmaz A, Barlas N, Kolankaya D. The effect of vitamin C on bisphenol A, nonylphenol and octylphenol induced brain damages of male rats. *Toxicology*. 2008; 249(1): 35-39.
49. Rice-Evans C, Miller N, Paganga G. Antioxidant properties of phenolic compounds. *Trends Plant Sci*. 1997; 2(4): 152-159.
50. Mourad IM, Khadrawy YA. The sensitivity of liver, kidney and testis of rats to oxidative stress induced by different doses of bisphenol A. *Life Science*. 2012; 2(2): 19-28.
51. Estakhr J, Javdan N. Spermatogenic activity of *Aloe vera* in adult male rats. *Pharmacologyonline*. 2011; 2: 886-889.
52. Rabab Fawzy Hindawy, Nagah Elsayed Mohammed Ali and Fatma Fawzi Hendawy. Ameliorative Effect of *Aloe vera* Gel on Tramadol Reproductive Toxicity In Adult Albino Rats. *Zagazig J. Forensic Med. & Toxicology*. 2019; 17 (2):71-83
53. Gupta Vivek Kumar, Park Uichang, Kim Eunsu, Kim Suheon, Siddiqi Nikhat J., Huh Yun Suk, Sharma Bechan. Antioxidative effect of *Aloe vera* against malathion induced neurotoxic response in Wistar rats. *Arabian Journal of Chemistry*. 2023; 16: 1-14
54. Keshavarzi Z, Rezapour TM, Vatanchian M, Zare Hesari M, Nabizade Haghghi H, Izanlu M, Sabaghian M, Shahveisi K. The effects of aqueous extract of *Aloe vera* leaves on the gastric acid secretion and brain and intestinal water content following acetic acid- induced gastric ulcer in male rats. *Avicenna J Phytomed*. 2014; 4: 137-143.
55. Park M-Y, Kwon H-J, Sung M-K. Dietary aloin, aloesin, or aloe-gel exerts anti-inflammatory activity in a rat colitis model. *Life Sci*. 2011; 88: 486-492.
56. Marzieh Shahryari, Bahram Bibak, Mohammad Khaksari, Zakiéh Keshavarzi, Neda Salmani, Sara Shirazpour, Fatemeh Alimahdi. Anti-edema effect of *Aloe vera* leaf extracts following traumatic brain injury: Role of pro-inflammatory cytokines. *AJP*. 2021; 11(4):380-393
57. Erten Akbel, Damla Arslan-Acaroz, Hasan Huseyin Demirel, Ismail Kucuk Kurt and Sinan Inced. The subchronic exposure to malathion, an organophosphate pesticide, causes lipid peroxidation, oxidative stress, and tissue damage in rats: the protective role of resveratrol. *Toxicol. Res*. 2018; 7: 503- 512
58. Sharma Y., Bashir S., Irshad M., Nag T. C. and Dogra T. D., Dimethoate-induced effects on antioxidant status of liver and brain of rats following subchronic exposure, *Toxicol.*, 2005;215:173–181.
59. Geeraerts F, Gijs G, Finne E, Crokaert R. Kinetics of fluoride penetration in liver and brain. *Fluoride*. 1986; 19: 108-12.
60. Shibata T, Watanabe M, Tanaka K, Wada K, Inoue Y. Dynamic changes in expression of glutamate transporter mRNAs in developing brain. *Neuroreport*. 1996; 7: 705-709.
61. Saritha V, Anil Kumar KR, Khanum F. Antioxidant and antibacterial activity of *Aloe vera* gel extracts. *Int J Pharmaceutical Bio Arch*. 2010; 4: 376-384.

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