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**Hanaa Khudair Abaas**

Department of Pathology,

College of Veterinary Medicine,

University of Baghdad, Iraq

**Samer Isam Sabeeh**

Department of Pathology,

College of Veterinary Medicine,

University of Baghdad, Iraq

## Pathological effect of estrogen on some internal organs of albino mice

**Hanaa Khudair Abaas and Samer Isam Sabeeh**

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### Abstract

The goal of this research was to evaluation the adverse effects of estrogen on the histopathological state of internal organs in mice. Twenty Swiss Albino mice, both male and female, were split into two groups at 21 days of age. The first group (G1) received daily oestrogen injections. The second group received olive oil as a control group. All mice were euthanized after six weeks, and specimens were collected from liver, kidney, spleen, heart, and brain. In contrast to the control group, mice that received therapeutic doses of estrogen demonstrated pathological lesions such as inflammation, haemorrhage congested blood vessels, necrosis, fibrosis, multiple granuloma lesions in internal organs, and proliferation of astrocytes and gliosis.

**Keywords:** Histopathology, liver, estrogen, hormones, toxic

### Introduction

Estrogens are biologically active hormones that are cholesterol derived and produced in human s and animals by the adrenal cortex, tests, ovaries and placenta. In plants, estrogenic compounds were also contained, (Hamid and Eskicioglu, 2012) <sup>[1]</sup>. Steroid estrogens may be identified as natural or synthetic hormone and may act as chemicals that inhibit endocrine.

Estrogen is the predominant sex steroid hormone in females, crucial for the development and control of secondary sex characteristics; estrone, estradiol, and estriol are the three main endogenous estrogens that signify hormonal activity. Estradiol is the most potent and common of them.

In all vertebrates, estrogens are synthesized (Ryan, 1982) <sup>[2]</sup>, and in some insects, (Mechoulam *et al.*, 2005) <sup>[3]</sup>. An appearance of estrogen in both of these, (insects and vertebrates) indicates a deep evolutionary history of oestrogenic sex hormones. Estrone (E1), estradiol (E2) and estriol (E3) are the three main naturally occurring sources of estrogen in females. The form of estetrol (E4) is developed during pregnancy.

Oestrogens circulate at lower concentrations in both men and women than androgens (Burger, 2002). Although oestrogen levels in males are substantially lower than those in females, oestrogen serves critical physiological functions (Lombardi *et al.*, 2001) <sup>[5]</sup>.

Estrogen, like other steroid hormones, permeate through the cell membrane and then attach to and activate oestrogen receptors (ERs) inside the cell. This process subsequently regulates the expression of multiple genes (Whitehead and Nussey, 2001) <sup>[6]</sup>. In addition, estrogens connect and activate receptors of estrogen and produce rapid-signal of membrane (mERs), (Soltysik, and Czekaj, 2013) <sup>[7]</sup>. Oestrogen is being synthesised from androgen by an enzyme known as aromatase, which is classified as CYP19A1 in the cytochrome P450 superfamily (Simpson *et al.*, 2002) <sup>[8]</sup>. The biological process of action of estrogen involves binding to its receptor to trigger a tissue response, with two different estrogen receptor proteins (ER $\alpha$  and ER $\beta$ ) exhibiting unique patterns of tissue expression (Mueller and Korach, 2001) <sup>[9]</sup>.

This is refer that sex hormones have different effects in different kidney area (Kwan *et al.*, 1996) <sup>[10]</sup>, and likely also in post UNX compensatory development. So efforts were undertaken to quantitatively assess the cross-sectional areas of the kidney zones, as well as glomerular volumes, glomerular counts, glomerular damage indicators, and glomerular injury mediators.

**Corresponding Author:**

**Hanaa Khudair Abaas**

Department of Pathology,

College of Veterinary Medicine,

University of Baghdad, Iraq

In an inflammatory bowel disease model. The oestrogen receptor (ER) is responsible for the inhibition of neutrophil aggregation in the intestine, as demonstrated by Harnish *et al.* (2004) <sup>[11]</sup>. The classic ER acts as a transcription factor based on ligand. Recent data suggests that signal transduction occurs by oestrogen receptors despite related to the regulation of transcriptional genes (Rajesh *et al.*, 2005) <sup>[12]</sup>, also suspected that the non genomic effects of estrogen are accelerated by these receptors which is located in or near the plasma membrane (Kelly and Levin, 2001). Isolate the effects of genomic processes facilitated by the nuclear oestrogen receptors. Studies continually use 17-estradiol (E2) membrane-impermeable combines, such as E2 conjugated to BSA (E2-BSA) (Stavis *et al.*, 1999) <sup>[14]</sup>. The present study has been aimed for investigating the effects of estrogen on the kidney, lung, liver, and intestine and heart tissues, in mice.

### Materials and Methods

Two groups were established by dividing twenty adult Albino mice (male and female) at 21 days of age. An s/c injection of 0.04 mg/kg b.w. of oestrogen was given to the first group (G1), which included 10 mice (5 males and 5 females). The ten mice in the second group—five male and five female—were given 0.1 ml of olive oil as a control group that received no treatment.

### Results

Histopathological alterations in rats administered estrogen daily for six weeks after therapy.

**Liver:** exhibits vacuolation of hepatic cells, characterized by enlarged nuclei and significantly dilated sinusoids containing inflammatory cells inside their lumens. Moreover, many micro granulomatous lesions originate by the accumulation of lymphocytes and macrophages inside the liver parenchyma (Figure 1, 2, 3).

**Kidney:** The lesion is defined by the accumulation of a significant material in the renal tubule (Figure 4). Furthermore, there is desquamation of the epithelial lining cells inside the renal tubules, followed by vascular congestion and significant acute cellular degeneration, along with moderate interstitial mononuclear cell infiltration (Figure 5).

**Lung:** There was congestion of pulmonary vessels, thickening of inter alveolar septa due to congestion of the alveolar capillaries and infiltration of the neutrophils (Figure 6, 7).

**Intestine:** There was diffuse necrosis of mucosa with shortening or loss of villi of small intestine. Intestinal mucosa showed increase in number of goblet cells with increase amount of mucin seen in the lumen. Focal infiltration of inflammatory cells especially neutrophils with few free RBC, in lamina propria of mucosa were also seen (Fig 8). Therapeutic Intervention Estrogen is administered as a solution at a dosage of 0.04 mg per kg of body weight by subcutaneous injection.

**Brain:** The cerebrum tissue slices exhibited significant dilatation and congestion of cerebral and meningeal blood vessels (Figure 9). Congestion of blood capillaries accompanied with perivascular and perineuronal edema. The cerebellum exhibited pyknosis of the nuclei in the granular layer cells of the folia, together with necrosis affecting a substantial proportion of those cells (Figure 10). Additionally, there is edema present between the granular and molecular

layers, along with degeneration of several Purkinje cells and total breakdown of others.

**Heart:** The histopathological examination of the heart revealed infiltration of inflammatory cells, mostly neutrophils, inside the muscle bundles (Figure 11).

**Stomach:** The histopathological examination of the stomach revealed infiltration of inflammatory cells, mainly neutrophils (Figure 12).

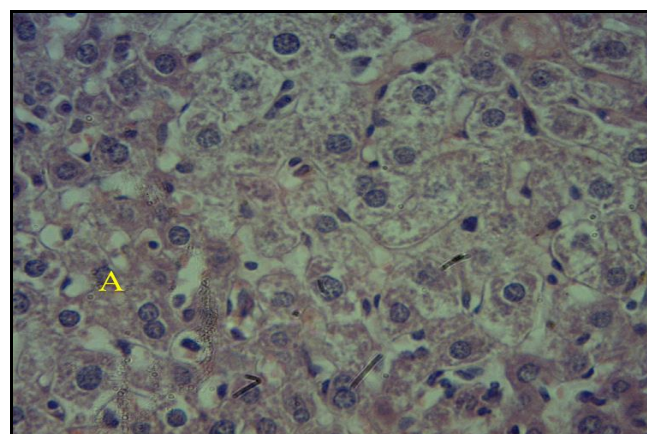


**Fig 1:** Histopathological section of liver of mice treated with 0.04 mg/kg.bw of estrogen showed vacuolation of hepatocytes (A) with centric nuclei. (H&E) stain 400 ×.

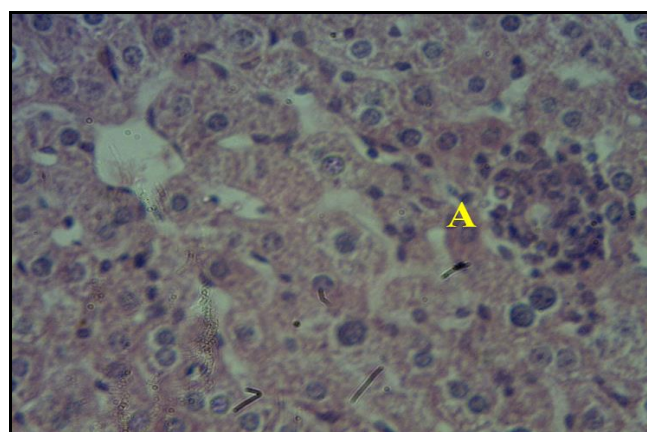


**Fig 2:** Histopathological examination of liver sections from mice administered 0.04 mg/kg body weight of estrogen revealed localized aggregation of lymphocytes and macrophages dispersed across the liver parenchyma (A). (H&E) stain 400 ×.

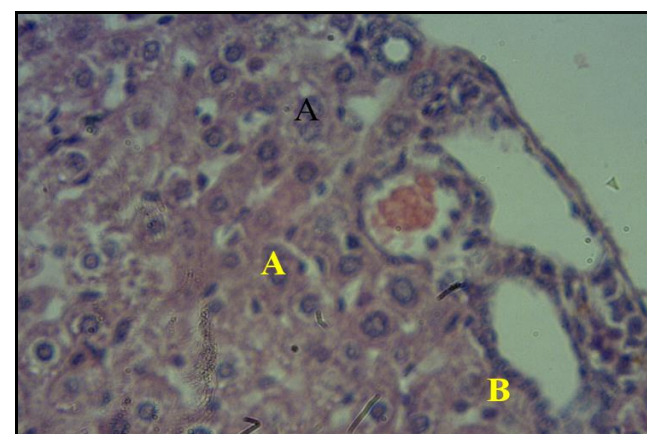


**Fig 3:** Histopathological examination of liver sections from mice administered 0.04 mg/kg body weight of estrogen revealed vascular congestion in the portal region (A) and infiltration of inflammatory cells, mostly neutrophils (B) (H&E) stain, 400×.

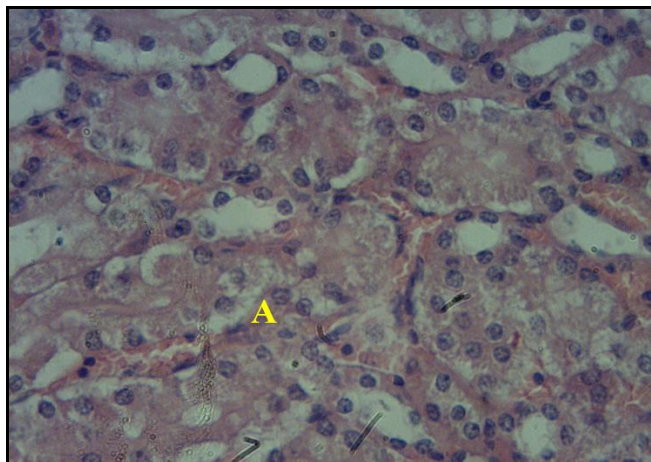


**Fig 4:** Histopathological examination of the kidneys of mice administered 0.04 mg/kg body weight of estrogen revealed the accumulation of a significant material inside the renal tubules (A). (H&E) stain, 400 $\times$ .

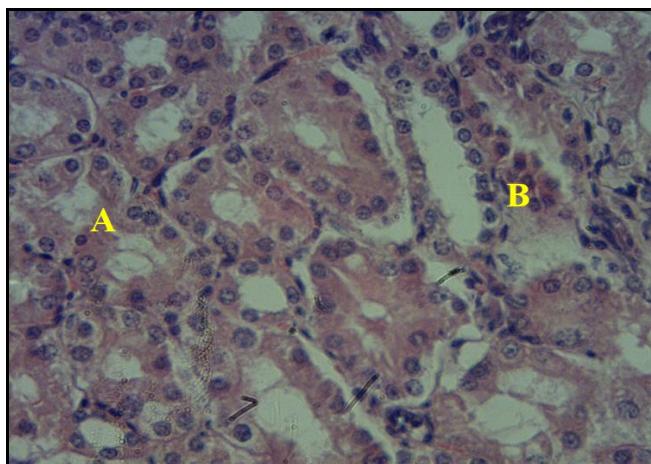


**Fig 5:** Histopathological section of kidney of mice treated with 0.04 mg/kg.b.w of estrogen showed acute cellular swelling of renal tubules (A) with interstitial mononuclear cell infiltration, (B). (H&E) stain, 400 $\times$

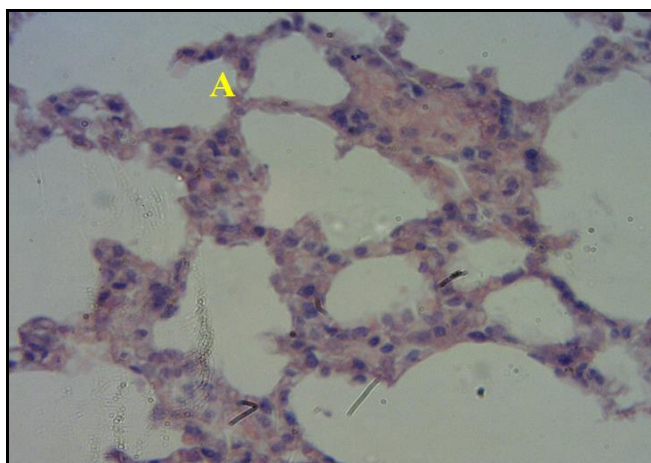


**Fig 6:** Histopathological section of lung of mice treated with 0.04 mg/kg. b.w of estrogen showed thickening of alveolar septa due to mononuclear cells aggregations & congestion of blood vessels (H&E) stain, 400 $\times$ .

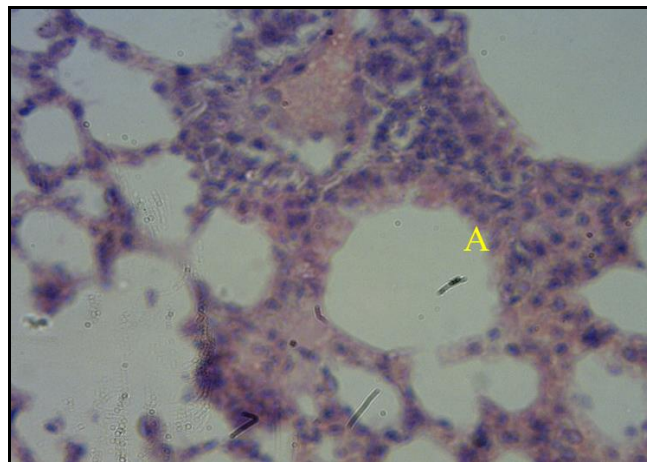


**Fig 7:** Histopathological section of lung of mice treated with 0.04 mg/kg. bw of estrogen showed perivascular lymphocytic cuffing (A) (H&E) stain, x400.

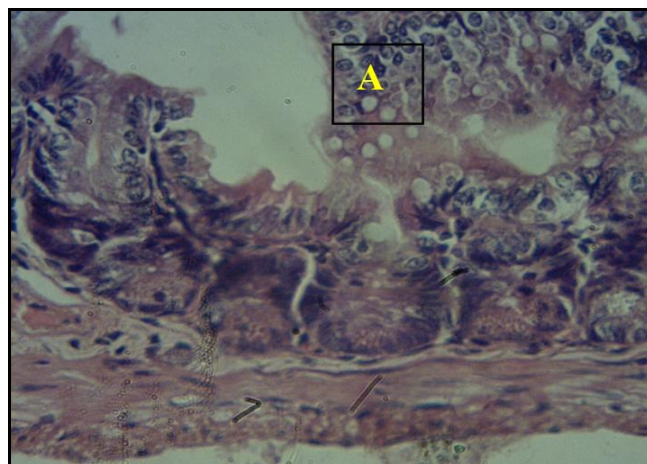


**Fig 8:** Histopathological section of intestine showed infiltration of inflammatory cells particularly neutrophils in the lamina propria & increase in number of goblet cells (A). (H&Estain), 400X.

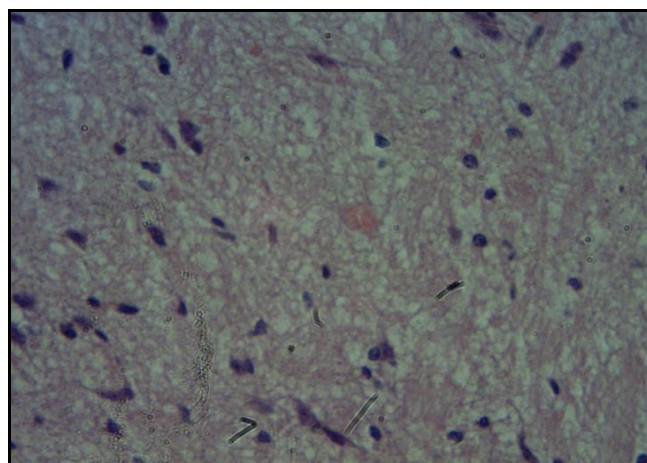


**Fig 9:** Histopathological section of cerebrum of mice treated with 0.04mg/kg. b.w estrogen showed edema and shrinkage of neurons containing pyknotic nuclei with loss of Nissels substance demyelination characterized by formation of large vacuoles (H&E) stain, 400 $\times$ .

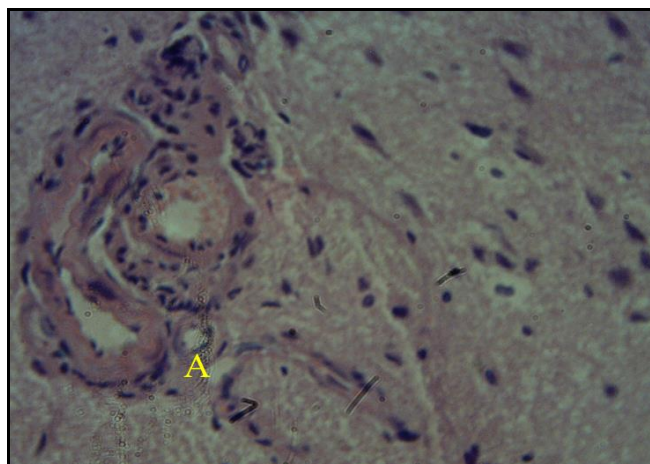


**Fig 10:** Histopathological section of cerebrium of mice treated with 0.04mg/kg. b.w estrogen showed mild perivascular lymphocytic cuffing of cerebral blood vessels (A). (H&E) stain, 400 $\times$ .

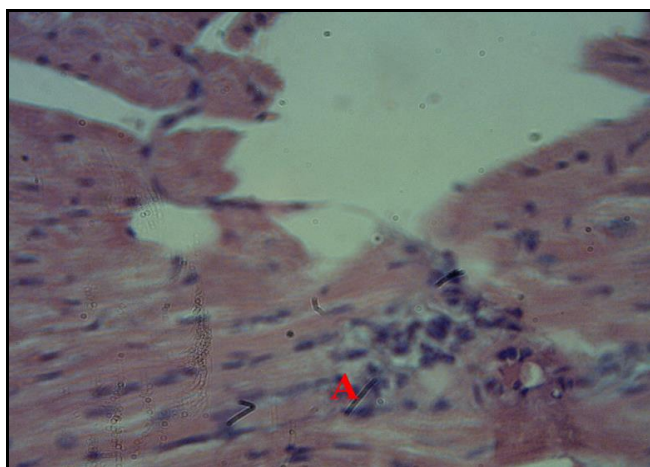


**Fig 11:** Histopathological section of heart of mice treated with 0.04 mg/kg. b.w of estrogen showed infiltration of inflammatory cells mainly neutrophils between muscle bundles (A). (H&E) stain, 400 $\times$ .

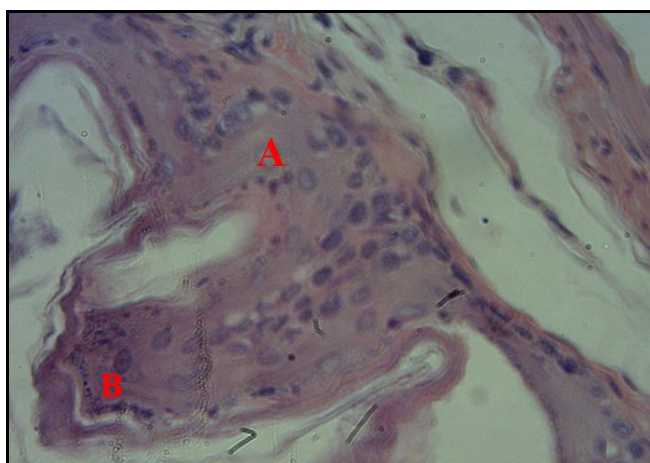


**Fig 12:** Histopathological section of stomach showed slight hyperkeratosis (A) of epithelial lining cells with sub epithelial inflammatory cells particularly neutrophils (B). (H&E) stain  $\times$ 400.

## Discussion

The present finding revealed different pathological lesions in the liver, kidney, lung and heart increasing its severity within 6 weeks post-treatment.

This may represent the primary lesions of estrogen resulting from interactions with the estrogen receptor (ER) and/or the synthesis of catechol estrogen (CE) by an oxidative stress-

mediated mechanism (Mobley and Brueggemeier, 2002) <sup>[15]</sup>. Specific bio molecules are destroyed under oxidative stress. These include (proteins, lipids and DNA), which is most important. Oxidative damage to DNA is important as it is not possible to synthesize entirely new molecules to repair the damage done, compared lipids.

Oxidative stress may result in increased damage that identified in different pathological situation, such as carcinogenesis, chronic inflammation, cardiovascular disease and neurodegenerative disease (Olinski, *et al.*, 2007) <sup>[16]</sup>. As with estrogens, the DNA damage is accelerated by stimulation of replication, that explain tumorigenesis result in DNA damage (Malins *et al.*, 1993) <sup>[17]</sup>, and this consistent with (Du and Gebicki, 2002) <sup>[18]</sup>. Reports indicate that lipid peroxidation precedes protein oxidation, with growing data suggesting that proteins are the initial and, under some circumstances, the exclusive extranuclear targets of oxidative stress.

Lipid hydroperoxides (LOOH), recognized as the earliest products of lipid peroxidation, may cause damage both *in vitro* and *in vivo* (Refsgaard *et al.*, 2000) <sup>[19]</sup>. However, the pathological changes in the internal organs particularly kidney may be due to toxic effects of estrogen metabolites, this evidence was supported idea, (Liehr, and Roy, 1990) <sup>[20]</sup>, who found that metabolic activation of estrogens, specifically, The free production of radicals by metabolic redox cycling between the quinone and hydroquinone forms of DES or catecholesterogen metabolites is hypothesized to contribute to the onset of carcinogenesis before hormone receptor-mediated cell transformation and tumor proliferation.

Free radicals are produced *in vitro* by metabolic redox cycling in the case of synthetic estrogen DES. In addition, the development of metabolic quinone, redox cycling, (Roy and Liehr 1992) <sup>[21]</sup>. In the case of steroid estrogens, Free radicals are generated by redox cycling between estrone-3,4-quinone and its equivalent hydroquinone during biochemical incubations and in cultured MCF-7 cells.

In which this metabolic activity causes DNA single strand, breaks (Nutter *et al.*, 1994) <sup>[22]</sup>. However, quinone metabolites may be formed and undergo metabolic redox cycling *in vivo* but they may be too unstable to be detected *in vivo* (Ball, and Knuppen, 1980; Floyd, 1990) <sup>[23, 24]</sup>, reported that kidneys are particularly vulnerable to free radical damage either induced by redox cycling of catechol estrogen substrates as outlined in this study or induced by toxic chemicals as demonstrated by others. This proposed mechanism is also corroborated by the observed DNA single-strand breaks in the kidneys, but not in the livers, of hamsters subjected to longterm treatment with either E or 4-OHE (Han and Liehr, 1994) <sup>[25]</sup>. And by increases in lipid hydro peroxide (Roy and Liehr 1992) <sup>[21]</sup> and in lipid-hydro peroxide-induced DNA adducts.

Oxidative stress is regarded as an important mechanism for cardiovascular disease development especially atherosclerosis (Singh and Jialal, 2006) <sup>[26]</sup>.

Many disorders of the cardiovascular system include CAD. Autoimmune thrombocytopenia is a bleeding disease and females with AITP have significantly higher oxidative stress levels compared to both female and male AITP controls (Kamhieh and Salama, 2014) <sup>[27]</sup>.

## Conflict of Interest

Not available

## Financial Support

Not available

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