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# Histopathological and Ultrastructural Changes Induced in the Renal Cortex of Male Rats by Gibberellic Acid

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## Abstract

**Objectives:** The present study was designed to evaluate the toxic effect of GA3 on the renal cortex of rats and to assess the possibility of recovery after GA3 withdrawal. **Materials and Methods:** Rats (n = 50) were classified into 5 groups: group 1 (control) received no treatment, animals belonging to group 2 and group 3 were respectively given GA3 at doses of 100 and 200part per million (ppm) daily for eight weeks in drinking water. Animals of recovery groups (group 4 and group 5) were remained for eight weeks without treatment after receiving 100 and 200 ppm of GA3 in drinking water for eight weeks respectively. Rats were dissected; kidney samples were collected and processed for histopathological and ultrastructural studies. **Results:** The renal cortex of GA3-treated rats exhibited its apparent toxic effect on renal corpuscles and renal convoluted tubules associated with fibrosis. These observations confirmed by the ultrastructure examination of renal cortical tissues. The Renal cortex from animals treated with 200 ppm GA3 revealed more severe structural changes. However, eight weeks of GA3 withdrawing has resulted in some regression of the pathological changes. **Conclusion:** GA3 has dose-dependent toxic effects. While stop giving of GA3 for eight weeks revealed incomplete recovery of its harmful effects. Therefore, exposure to GA3 should be limited.

**Keywords:** Plant Growth Regulators, Gibberellic Acid Toxicity, Renal Cortex, Ultrastructure, Rats

## 1. Introduction

The plant growth regulators (PGRs) are among the several chemicals that are widely used in agriculture nowadays. It started to be used in the 1930s [1]. PGRs regulate plant growth, they are also known as phytohormones or plant growth hormones [2]. According to the American Society of Agricultural Science and gibberellins are one of the six major classes of plant growth regulators [3]. In many countries, gibberellic acid (GA3) is used to increase

the growth of some vegetables such as pepper, tomatoes, and olive and fruits such as date palm, grapes and strawberries [4].

Additionally, Hazards of these regulators placed into the environment may soon exceed those of insecticides [5]. The World Health Organization listed GA3 as plant growth regulators related to pesticides. GA3 could possess a risk to those professionally exposed, as well as the general population via the consumption of contaminated food products [6]. The U.S. Environmental Protection Agency (EPA) determined its use to be only allowed in low doses [7]. GA3 is one of the most active hormones of gibberellins. It affects many mechanisms of plant growth including stem elongation by stimulating cell division and elongation and used to promote seed germination, flowering, proliferation, and fertilization in a wide variety of crops [8].

Several studies demonstrated that the chronic consumption of gibberellic acid increased tumor formation and hepatocellular carcinomas in 16% of the animals [9], and also induced breast and lung adenocarcinomas in mice [10]. Several studies indicate that the oxidative stress induced by GA3 results in releasing of free radicals causing cell damage in adult rat organs such as the liver, kidney and heart [11].

Compared with other organs, the kidney is uniquely susceptible to chemical toxicity, because of its disproportionately high blood flow and due to its complexity both anatomically and functionally. It extracts and concentrates toxic substances, so glomerular, tubular and renal interstitial cells frequently encounter significant concentration of toxins and their metabolites, which can induce adverse changes in the structure and function of the kidney [12].

The extensive use of the GA3 in agriculture making it an important project to investigate its possible hazard effects on the kidney which consider one of the main target organs for different xenobiotics. Therefore, the present study was conducted to assess the toxic effects induced in the renal cortex of male rats by administration of two different doses of GA3 for eight weeks, and also to detect the effects of GA3 withdrawing on the affected organs after eight weeks of treatment.

# 2. Materials and Methods

## 2.1. Chemicals

Gibberellic acid 5% (Gibaifar) was obtained from AIFARAGROCHIMICASRL Via Bazzano, 12 6019 Ronco Scrivia (Genoa) Italy.

## 2.2. Preparation of GA3 Doses

Two different doses of GA3 were prepared by dilution of 2 ml of 5 % GA3 (equivalent to 100 mg) and 4 ml of 5 % GA3 (equivalent to 200 mg) with tap water till 1000 ml to obtain 100 ppm and 200 ppm of GA3 respectively according to [13–14].

## 2.3. Experimental Animals

This study was conducted on 50 adult male albino rats (*Rattus norvegicus*), weighting (170–200 g) were obtained from an animal house in College of Veterinary Medicine,

Zagazig University, Zagazig, Egypte. Rats stayed in the ventilated cage, fed ad libitum with a standard diet, supplied with free access to water. They were kept for 14 days under suitable laboratory conditions for adaptation before the initiation of the experiment.

## 2.4. Experimental Design

Animals were randomly divided into 5 groups (10 rats each): group 1 kept without treatment (control), animals of group 2 and group 3 received GA3 at doses of 100 and 200 ppm in drinking water daily for 8 weeks respectively according to [13–14], group 4 (recovery of low dose GA3 group) 100 ppm of GA3 was given in rats drinking water daily for eight weeks, and then withdrawn for another 8 weeks and group 5 (recovery of high dose GA3 group) animals received GA3 at a dose of 200 ppm daily in drinking water for eight weeks, and then GA3 administration was stopped for another 8 weeks. On completion of the experiment, rats were sacrificed under ether anesthesia, kidneys were removed and immediately processed for histopathological, and ultrastructural examination.

## 2.5. Histopathological Studies

Kidney specimens from all groups were fixed in 10% neutral formal saline, embedded in paraffin wax. Sections of 5 µm thicknesses stained with Harri's hematoxylin and eosin [15]. Histochemical changes were demonstrated by Masson's trichrome stain [15] for the detection of the collagen fibers. All stained sections were examined under a light microscope.

## 2.6. Ultrastructural Studies

Renal cortex specimens were processed for ultrastructural examination by transmission electron microscopy (TEM); samples were sliced into small pieces of ~1 $mm^3$ and fixed for 24–48 hr in 2.5% glutaraldehyde. Then, phosphate buffer (pH 7.4) was used for washing specimens 3–4 times for 20 min. every time and fixed in a buffered solution of 1% osmium tetroxide at 4 °C for 2 hr. After dehydration in ascending grades of ethyl alcohol, the specimens were cleared in two changes of propylene oxide, and after that embedded in Epon resin [16]. Semi-thin sections (~1 µm thick) were stained with 1% toluidine blue stain and examined by using a light microscope. Areas of interest were selected and the blocks were trimmed accordingly. Ultrathin sections (60–70 nm) were cut using an ultra-microtome (MT6000-X L RMC, Inc.), mounted on copper grids and double-stained with lead citrate and uranyl acetate and [17] Grids were examined and photographed by TEM (JEOL JEM-1010, Japan) operated at 60–70 kV, Regional Center for Mycology and Biotechnology (RCMB), Al-Azhar University.

# 3. Results

## 3.1. Histopathological Studies

Histopathological examination of the renal cortex of control rats (group1) showed a well-developed architecture of renal corpuscles, glomeruli, Bowman's capsule, proximal

and distal convoluted tubules (Figure 1a) with fine collagenous fibers around the renal corpuscle and convoluted tubules (Figure 2a).

The renal cortex of group 2 (low dose of GA3) showed enlarged glomerulus with focal adhesion between glomerular tuft and Bowman's capsule, detached tubular epithelium and desquamated cellular debris (Figure 1b). Slightly increased collagen fibers were observed around the glomerulus and renal tubules (Figure 2b).

Examination of the renal cortex of rats from group 3 (high dose of GA3) revealed distended glomeruli, necrotic and vacuolated tubular epithelial cells (Figure 1c), atrophied and lobulated glomeruli, inflammatory cells infiltration, interstitial hemorrhage and cast in the tubular lumen (Figure 1d). There were highly increased intraglomerular mesangial matrix collagen fibrils associated with fibrosis around the renal corpuscle and convoluted tubules (Figure 2c).

The renal cortex of group 4 (recovery of low dose of GA3) showed marked regression in the toxic effect of GA3, the glomerular capillary tuft and some proximal convoluted tubules were more or less normal in shape but, congested blood capillaries of glomerulus and interstitial hemorrhage were still noticed (Figure 1e) with few collagen fibers in periglomerular and peritubular areas (Figure 2d).

Partial recovery was observed in renal cortices of treated rats in group 5 (recovery of a high dose of GA3), however, dilatation of convoluted tubules exfoliation of epithelial cells and degeneration of glomerular capillary tuft were still seen (Figure 1f). Slightly decreased collagen fibers were detected in the glomerular mesangial matrix and around the renal corpuscles, however, some fibrotic convoluted tubules were observed in the renal cortical tissue (Figure 2e).

## 3.2. Ultrastructural Studies

Ultrastructural examination of the renal cortex of control rats (group 1) revealed normal renal corpuscles, glomerular blood capillaries, endothelial cells, mesangial cells and podocytes have primary and secondary foot processes in close contact with the glomerular basement membrane (Figure 3a). Epithelial lining cells of the proximal convoluted tubules appeared with euchromatic nuclei, tall apical microvilli and elongated mitochondria within basal enfoldings (Figure 4a). Distal convoluted tubules showed wide tubular lumen lined by epithelial cells have round euchromatic nuclei; few short apical microvilli and basal infoldings enclose elongated mitochondria (Figure 5a).

The renal cortex of group 2 (low dose of GA3) showed thickening of glomerular capillary endothelium, apoptotic mesangial cell, the endothelial cell has electron-dense nucleus and podocytes with swollen and fused secondary foot processes (Figure 3b). Cells lining the proximal convoluted tubules appeared small with condensed heterochromatin nucleus, cytoplasmic vacuolation, swollen mitochondria, large lysosomes and disrupted brush border (Figure 4b). Distal convoluted tubules exhibited narrow tubular lumen; epithelial cells have shrunken nuclei and devastated mitochondria within disorganized basal infoldings (Figure 5b).

Renal corpuscles in group 3 (high dose of GA3) showed glomerulus with, focal thickening of basement membrane flattened and distorted secondary foot processes

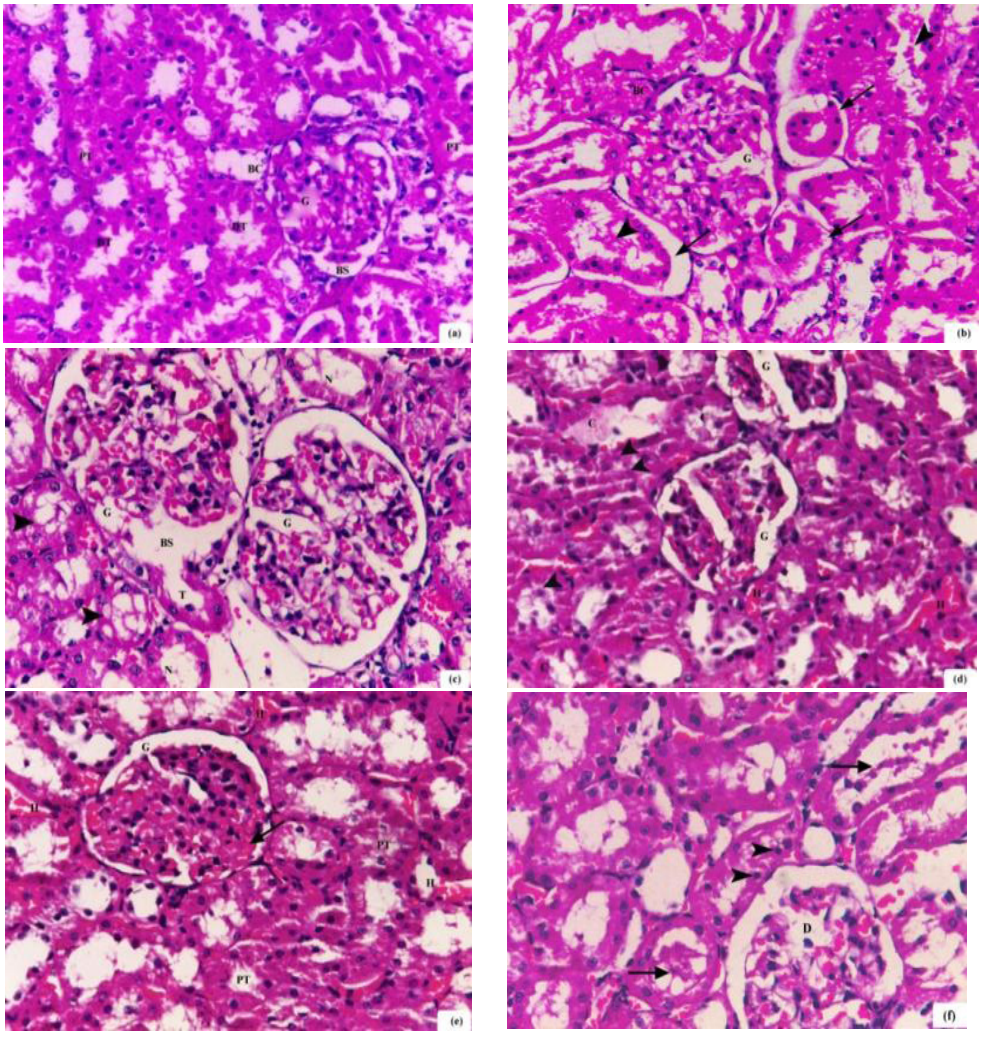


**FIGURE 1.** (a–f): Renal cortex of control and different treated groups stained with hematoxylin and eosin, (a) Group 1 (control) showing normal architecture of renal corpuscles formed of glomerular capillary tuft (G) surrounded by Bowman's capsule (BC)with narrow Bowman's space (BS), proximal convoluted tubules (PT) and distal convoluted tubules (DT). (b) Group 2 showing enlarged glomerular tuft (G) adheres to Bowman's capsule (BC), the detached tubular epithelium (arrows) and desquamated cellular debris (arrowheads). (c,d) Group 3 showing epithelial cells have cytoplasmic vacuolation (arrowheads) and necrosis (N), distended glomeruli (G), and ruptured tubule (T) penetrated in Bowman's space (BS), (c). Atrophied and lobulated glomeruli (G), inflammatory cells infiltration (arrowheads), interstitial hemorrhage (H) and tubular lumen contains cast (C), (d). (e) Group 4 showing a marked recovery in glomerular capillary tuft (G) and some proximal convoluted tubules (PT) however, congested blood capillaries (arrow) of the glomerulus and interstitial hemorrhage (H) are still seen. (f) Group 5 showing a partial recovery in the renal cortex, however, dilatation of tubules with exfoliated epithelial cells (arrows) and degeneration (D) of glomerular capillary tufts are still detected. (a–f) H&Ex400.

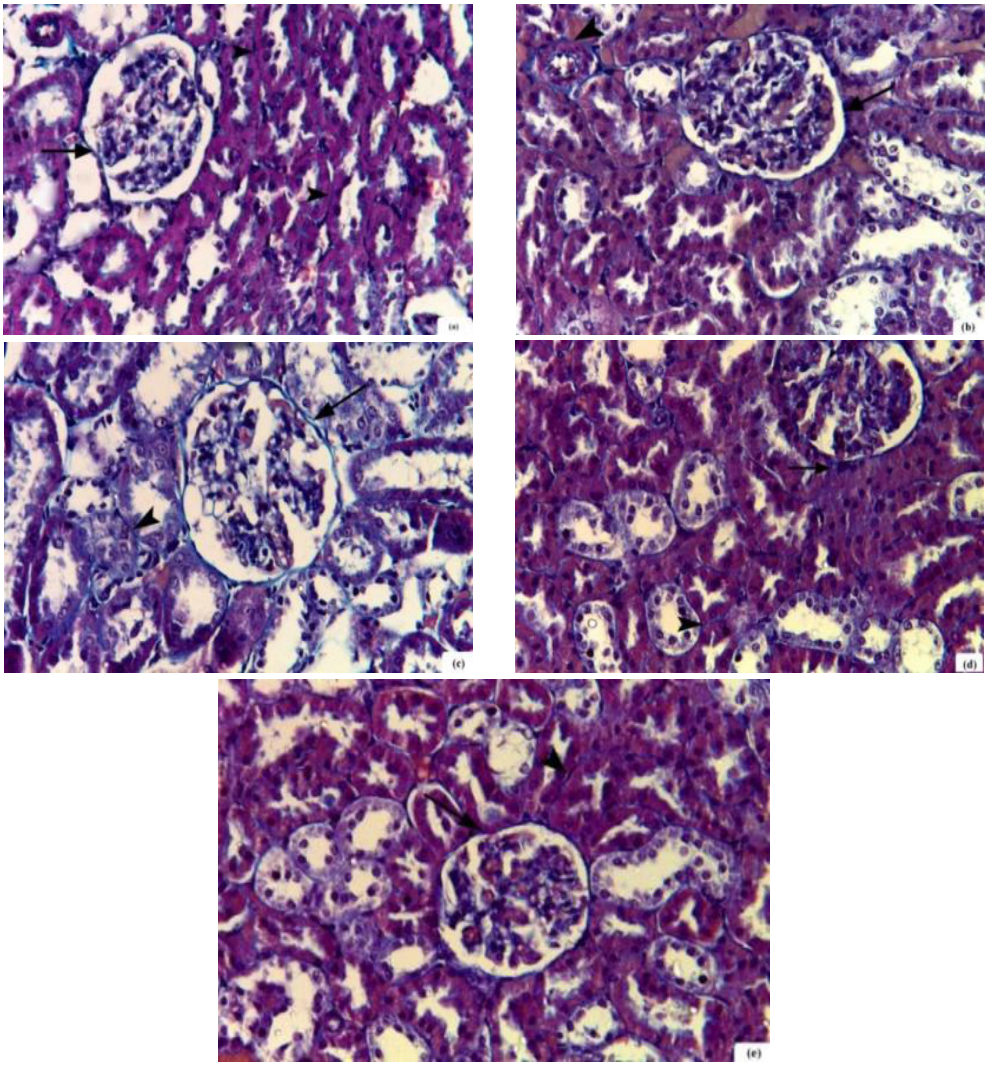

**FIGURE 2.** (a–e): Renal cortical tissue of control and different treated groups stained with Masson's trichrome stain, (a) Group 1 showing few intraglomerular mesangial collagen fibrils and fine collagenous fibres around the renal corpuscle (arrow) and convoluted tubules (arrowheads). (b) Group 2 mild increases in collagen fibres surrounding the glomerulus (arrow) and convoluted tubules (arrowhead). (c) Group 3 highly increased intraglomerular mesangial collagen fibrils with fibrosis around the renal corpuscle (arrow) and renal tubules(arrowheads). (d) Group 4 showing nearly normal distribution of few collagen fibres in periglomerular (arrow)and peritubular (arrowheads) areas. (e) Group 5 showing slightly decreased collagen fibres in the glomerular mesangium and around the renal corpuscles (arrow) but some fibrotic convoluted tubules (arrowheads) are still detected. (a–e) Masson's trichrome stain X400.

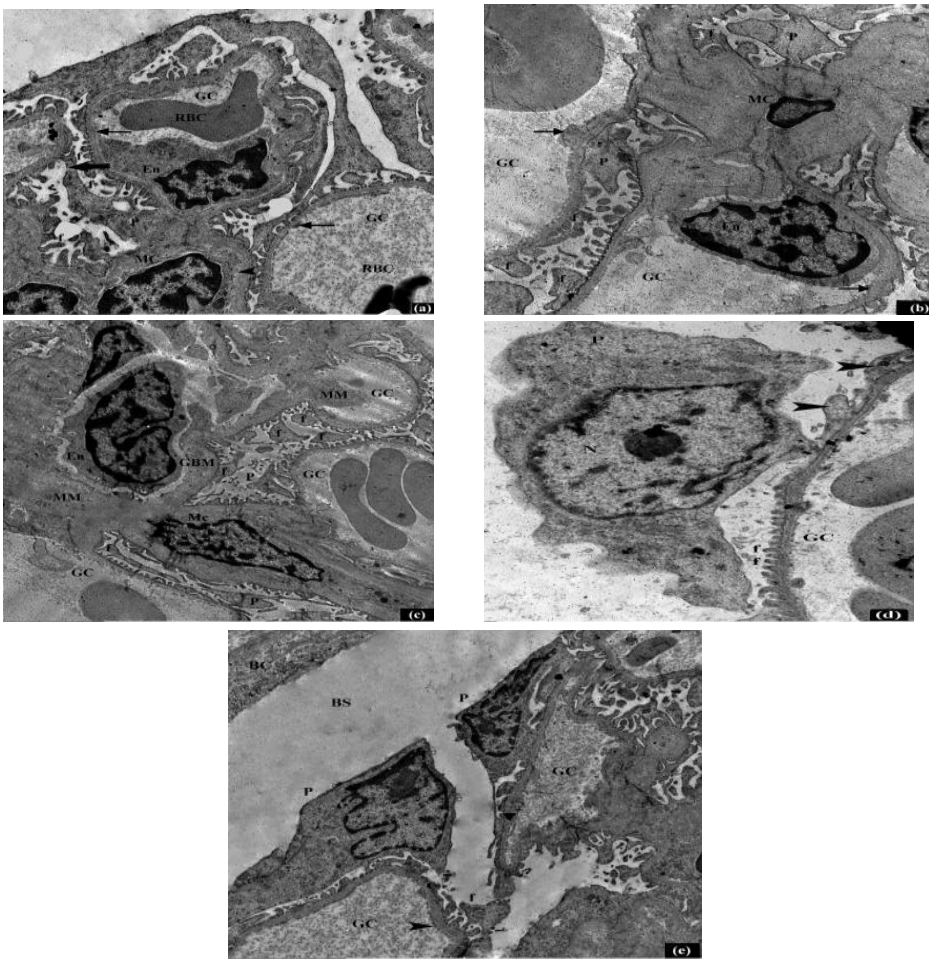


**FIGURE 3.** (a–e): Transmission electron micrographs of the renal cortex showing a part of glomerular lobule of control and different treated groups, (a) Group 1 showing normal architecture of glomerular capillaries (GC) lined by fenestrated endothelium (arrows) containing red blood cells (RBC), glomerular basement membrane (arrowheads), endothelial cells (En), mesangial cells (MC), primary (thick arrow) and secondary (f) foot processes of podocyte (P), X10000. (b) Group 2 showing glomerular capillaries (GC) have thickened endothelium (arrows), the electron-dense nucleus of endothelial cell (En), swollen and fused secondary foot processes (f) of podocytes (P) and apoptotic mesangial cell (MC), X12000. (c) Group 3 showing degenerated podocyte (P) with flattened and distorted secondary foot processes (f), swollen endothelial cell (En), malformed mesangial cell (MC) with increasing of mesangial matrix (MM) encroaching on the glomerular blood capillary lumen (GC) and focal thickening of glomerular basement membrane (GBM), X8000. (d) Group 4 showing marked recovery of glomerular blood capillaries (GC), slightly normal podocyte (P) with euchromatic nucleus (N) and nearly normal secondary foot processes (f) however, some of them are still swollen and fused together (arrowheads), X10000. (e) Group 5 showing partial recovery of glomerular capillaries (GC) with slightly normal endothelium(arrowhead), and more or less normal podocytes (P) however, Bowman's capsule (BC) have extensively wide Bowman's space (BS), also flatted and fused secondary foot processes (f) are still noticed, X8000.

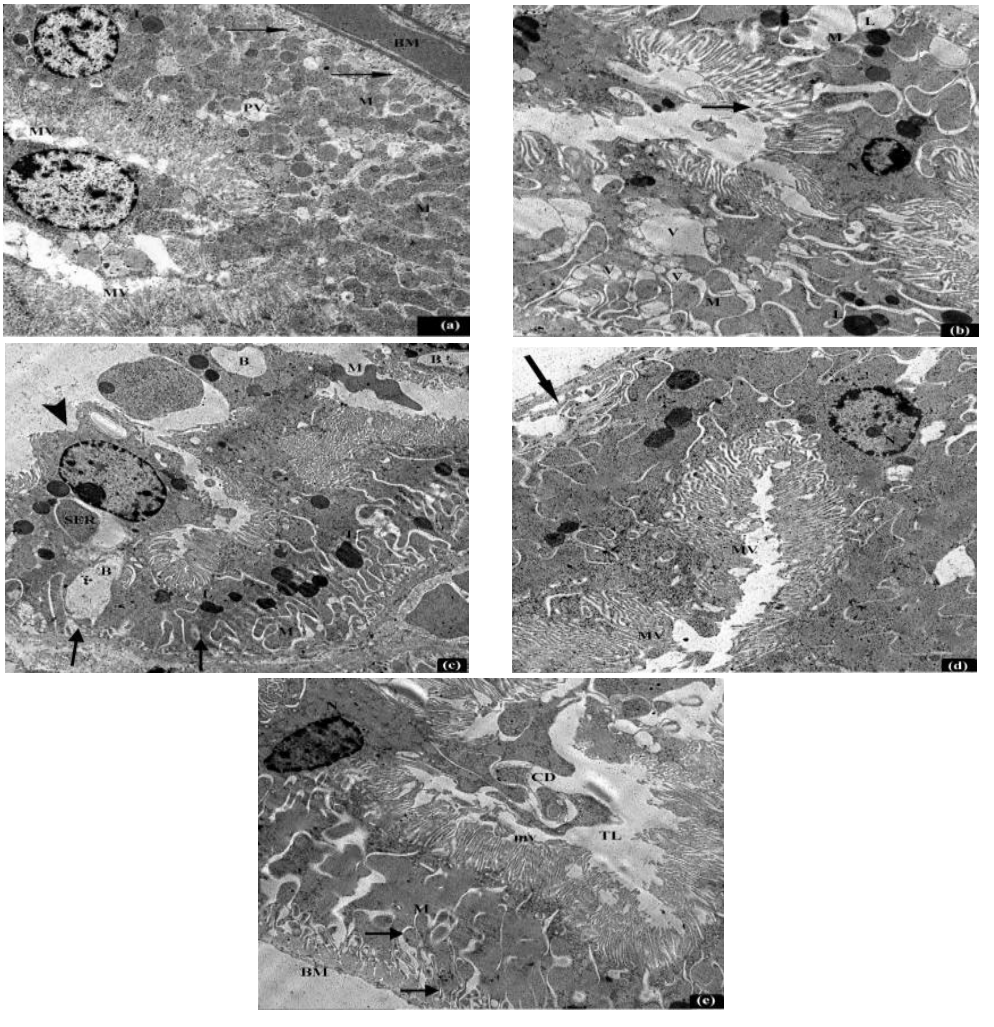


**FIGURE 4.** (a–e): Transmission electron micrographs of the renal cortex showing apart of proximal convoluted tubule of control and different treated groups, (a) Group 1 showing lining cells with euchromatic nuclei (N), numerous tall apical microvilli (mv), elongated mitochondria (M) within basal enfoldings (arrows), tubular basement membrane (BM), pinocytosis vesicles (PV) and lysosomes (L), X5000. (b) Group 2 showing epithelial cells with small and condensed peripheral heterochromatin nucleus (N), cytoplasmic vaculation (V), swollen mitochondria (M), large lysosomes (L) and disrupted brush border (arrow), X8000. (c) Group 3 showing degenerative changes in tubular cells (arrows), cytoplasmic blebs (B), pleomorphic and deteriorated mitochondria (M), increased number and size of electron-dense lysosomes (L), aggregated and dilated smooth endoplasmic reticulum (SER) and loss of apical microvilli(arrowhead), X5000. (d) Group 4 shows marked recovery in epithelial cells manifested by the spherical euchromatic nucleus (N) and normal microvilli (MV) of brush border, but, disrupted basal infoldings (arrow) is still seen, X8000. (e) Group 5 showing partial recovery in basal infoldings (arrows) resting on tubular basement membrane (BM), and accommodate a few more or less normal mitochondria (M) and apical microvilli (mv) appear slightly normal however, cellular debris (CD) in tubular lumen (TL) and irregular electron-dense nucleus (N), are detected, X6000.

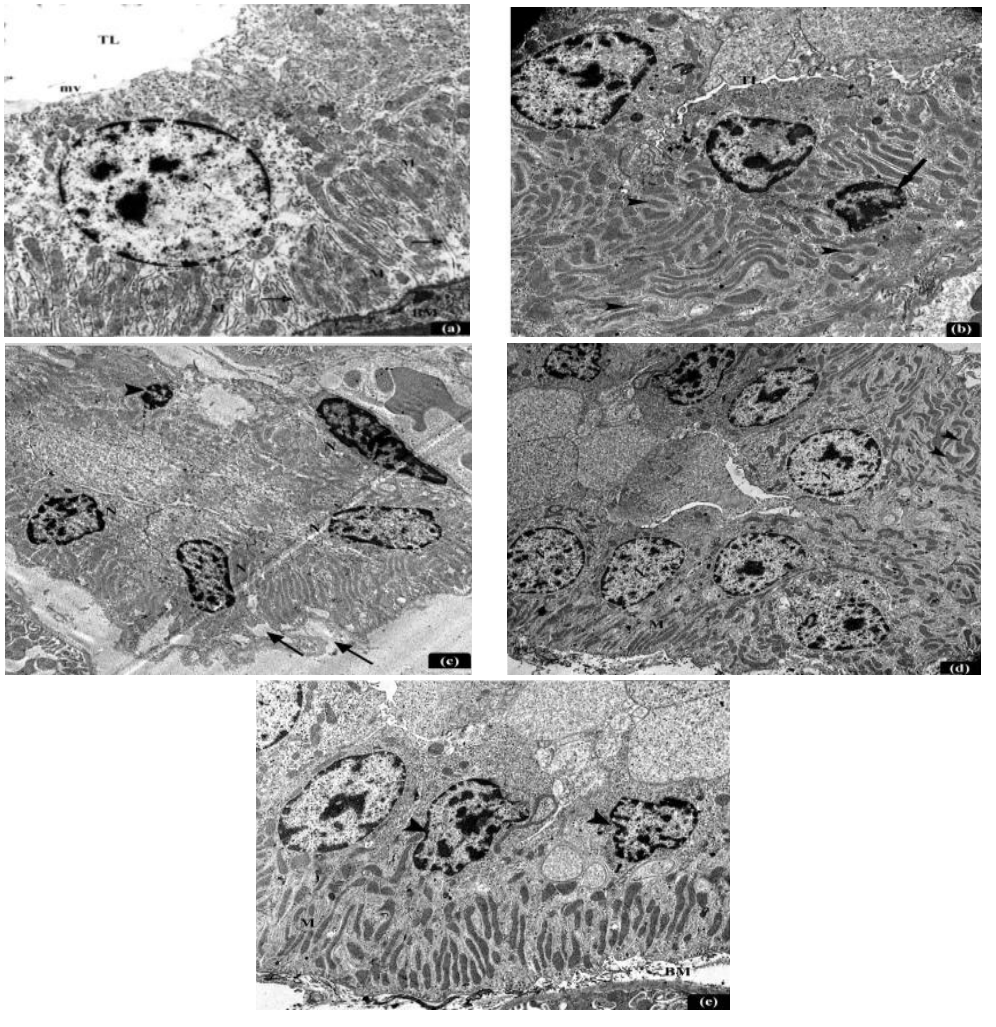


**FIGURE 5.** (a–e): Transmission electron micrographs of the renal cortex showing apart of distal convoluted tubule of control and different treated groups, (a) Group 1 showing wide tubular lumen (TL) lined by epithelial cells, with round euchromatic nuclei (N), few short apical microvilli (mv) and elongated mitochondria (M) lodged in the basal infoldings (arrows) perpendicular to basement membrane (BM), X8000. (b) Group 2 narrow tubular lumen (TL), epithelial cells showing shrunken nucleus with condensed heterochromatin (arrow), the devastation of some mitochondria (arrowheads), X6000. (c) Group 3 showing demolished epithelial cells with irregular electron-dense nuclei (N) and apoptotic nucleus (arrowhead), focal degeneration of tubular basement membrane and basal infoldings (arrows), X5000. (d) Group 4 showing a marked recovery in the tubular cells, nuclei (N) and mitochondria (M) appear nearly in restored condition, few numbers of mitochondria acquire bizarre shapes (arrowheads), X4000. (e) Group 5 showing a partial recovery in epithelial cells have a euchromatic nucleus and nearly normal appearance of basal infoldings enclose elongated mitochondria (M), however, disrupted tubular basement membrane (BM) and condensed chromatin in irregular nuclei (arrowheads) are still noticed, X6000.

of the podocyte, swollen endothelial cells and malformed mesangial cell (Figure 3c). Epithelial cells of proximal convoluted tubules revealed degenerative changes manifested by cytoplasmic vacuolation, pleomorphism and deterioration of mitochondria, numerous electron-dense lysosomes, aggregation and dilatation of smooth endoplasmic reticulum and loss of apical microvilli (Figure 4c). Focal degeneration of tubular basement membrane and basal infoldings, demolished cells with irregular electron-dense and apoptotic nuclei, were demonstrated in distal convoluted tubules (Figure 5c).

Ultrathin sections of the renal cortex of group 4 (recovery of a low dose of GA3) showed marked recovery as in most of the glomerular blood capillaries, nuclei and secondary foot processes of podocyte appeared nearly normal but, some of these processes were still swollen and fused together (Figure 3d). Cells lining proximal convoluted tubules exhibited apparently spherical euchromatic nucleus and slightly normal microvilli (MV) of brush border however, disrupted basal infoldings were still detected (Figure 4d). Distal convoluted tubular epithelium showed an apparent decrease in the damaging effect of GA3 as in most of nuclei and mitochondria appeared nearly in restored condition but, some mitochondria acquired bizarre shapes (Figure 5d).

Renal cortices of rats from group 5 (recovery of high dose of GA3) showed signs of partial recovery, endothelium of glomerular blood capillaries displayed slightly normal appearance, the glomerular tufts surrounded by Bowman's capsule and podocytes are more or less normal in shape, however, flatted and fused secondary foot processes of podocytes and wide Bowman's space were still observed (Figure 3e). Partial improvement was observed in the epithelial lining of proximal convoluted tubules, a few more or less normal mitochondria were lodged in basal infoldings and the brush border showed slightly normal apical microvilli, but, irregular and electron-dense nucleus and cellular debris in tubular lumen were detected (Figure 4e). Distal convoluted tubular cells showed an euchromatic nucleus and nearly normal appearance of basal infoldings enclose elongated mitochondria, however, disrupted tubular basement membrane and some irregular nuclei with condensed chromatin were still seen (Figure 5e).

## 4. Discussion

In recent years, significantly increased use of plant growth hormones in agriculture, makes it an interesting subject to detect its possible harmful effects [18–19]. Gibberellic acid (GA3) is produced by a naturally-occurring fungus in large vats [7]. Although it is extensively used in agriculture; little is known about its potential hazardous effects on mammalian tissues. So, the present work was designed to investigate the toxic effect of GA3 on the histological and ultrastructural pattern of the renal cortex in adult male albino rats and also to determine the effects of the withdrawal of GA3 on the affected structures following 8 weeks of follow up [20].

In the present study, light microscopic examination of the renal cortex from control rats revealed the normal architecture of renal corpuscles, glomeruli, Bowman's capsules and convoluted tubules. These findings were similar to those of other workers. A few collagen fibers were detected in the interstitium around the renal corpuscles and convoluted tubules. A study reported similar results [21–23].

Recent reports indicated that the toxicity of many xenobiotics, including PGRs, is associated with releasing of reactive oxygen species (ROS) which penetrates the tissues, causing several pathophysiological aberrations [24] and induce damage in every major cellular component, including membranes, carbohydrates, lipids and DNA [25].

The present investigation by a light microscope showed that GA3 induced different histological changes in the renal tissue. The renal cortex of low dose GA3-treated rats showed swollen glomerulus, degenerated renal tubules, detached tubular epithelium and desquamated cellular debris accompanied by a slight increase in collagen fibers. These results were in accordance with those recorded by other workers [26] and could be explained by the report of previous authors who suggested that glomerular and tubular degeneration and necrosis attributed to oxidative stress and lipid peroxidation which was detected by increased malondialdehyde level in the kidney. Oxidative stress was considered as one of the molecular mechanisms of toxicity. It occurs as a result of the disturbing effects of xenobiotics on the antioxidant enzyme system.

The renal cortex of high dose GA3-treated rats showed distended glomeruli, leucocytic infiltration and interstitial inflammatory response in the form of congestion of blood capillaries and interstitial hemorrhage. The same changes were observed in the kidney treated with gibberellic acid [27–28] and in the kidney treated with other plant regulators. Previous studies concluded that inflammatory reactions were considered as a prominent response of the body tissue facing any harmful effects [29]. Chronic inflammation plays a significant role in the induction of oxidative stress. Chronic kidney disease causes a low-level chronic inflammatory process that becomes apparent at the beginning of the disease [30]. Methemoglobinuria results from interstitial hemorrhage and congestion of blood capillaries [31]. This finding could explain the serious cases of hematurea that reported in workers engaged in the manufacturing and packaging of agricultural pesticides [32]. Furthermore, many convoluted tubules in the renal cortex showed necrotic epithelial cells, cytoplasmic vacuolation in tubular cells. In accordance with these results [4] stated that vacuolization of cytoplasm is one of the important primary responses to all cell injury forms. It indicates increased permeability of cell membranes resulting in an increase of intracellular water. As water sufficiently aggregates within the cell, it induces cytoplasmic vacuolization. Atrophied and lobulated glomeruli, ruptured tubules and cast in tubular lumen were detected in the present study. The sensitivity of the glomeruli is due to the large surface area of the glomerular capillaries which renders them susceptible to damage from immune complexes and circulating toxins [33]. Glomerular atrophy in the treated animals of this study may be attributed to the small size of glomeruli accompanied by fibrosis. This explanation is in agreement with [34] who reported that gibberellic acid was highly injurious to the kidney and referred the cystic glomerular atrophy to the small size of some glomeruli within the dilated Bowman's space. Other researchers attributed the pathogenesis of this injury to periglomerular fibrosis [35]. Blockage by casts is one mechanism by which proteinurea could injure tubules, although a toxic effect on tubule cells has not been completely excluded [36].

Ultrastructural examination of the renal cortex of low dose GA3-treated rats showed thickening of glomerular capillary endothelium with affected podocytes, endothelial cells, and mesangium. These observations were in accordance with that recorded by [37].

The glomerular affection was aggravated in high dose GA3-treated rats; the glomerular basement membrane appeared with a focal thickening. In harmony with this research results mentioned that the thickening of the glomerular basement membrane results in a disturbance of glomerular outflow that leads to cystic changes in Bowman's space.

In the present study, treatment with GA3 resulted in variable ultrastructure changes including marked degeneration of podocytes associated with fusion, swelling, flattening and distortion of secondary foot processes. The abnormal architecture of the foot process was referred to as effacement which is an invariable feature of proteinuric glomerular diseases [38–39]. The podocyte is the primary target of injury in several forms of glomerular infection. Podocyte injury is involved in both the onset and progression of glomerular diseases [40].

In the current study, an electron microscopic examination of the renal cortex of treated rats showed loss and/or disruption of apical microvilli of lining cells of the proximal tubules. In [41] reported that loss of polarity of polarized epithelia of proximal convoluted tubules due to its contact with toxins resulted in their ischemia, then eventual necrosis. Our results showed swollen and devastated mitochondria and apoptotic nuclei appeared in the epithelial lining cells of the renal tubules. The same alterations were observed by other workers who found swollen mitochondria in the renal tubules of GA3 treated rats [25], and deformed mitochondria in the hepatocytes of the liver tissue. Several studies disclosed that mitochondrial dysfunction contributed to apoptosis via the production of reactive oxygen species [42–43].

In the present work, the epithelial lining cells of renal convoluted tubules revealed large lysosomes in low dose GA3-treated rats and numerous electron-dense lysosomes in high dose GA3-treated animals. An excess number of lysosomes with variable size reflected accelerated intracellular degradation of macromolecules [44]. In the present study, the epithelial lining of the proximal convoluted tubular cells of high dose GA3-treated animals showed aggregated and dilated smooth endoplasmic reticulum. Similar changes were detected in the pancreatic acinar cells of GA3-treated rats that appeared with dilated rough endoplasmic reticulum [45]. The dilatation of rough endoplasmic reticulum indicated increased endoplasmic reticulum stress [46].

In the current study, the withdrawal effect of GA3 treatment on renal cortex was also investigated. Recovery of some renal convoluted tubules was observed where ultrastructure alterations were less evident than those in the treated animals. This recovery may be attributed to the contribution of injured renal convoluted tubules that do not degenerate or detach from the basement membrane to the regeneration of the tubular epithelium and the restoration of overall renal function [47]. In addition, the tubular epithelial cells showed most of the mitochondria appeared in nearly restored condition. In agreement with current research results, Kimball [48] observed that mitochondria almost retained their normal appearance suggesting increased active detoxifying mechanisms in animal tissues which might need a longer period of withdrawal to escape from the toxic effect of GA3. In [49] reported that feeding 2 weeks old broiler chicks on gibberellic acid (GA3)-containing diets for 3 weeks led to several histological lesions in different organs. Two-week withdrawal periods did not ameliorate the adverse effects of GA3. Also, the toxic effects of GA3 were dose-dependent. While,

8 weeks period of follow up after the GA3 stoppage, was insufficient for the complete recovery of these toxic effects [50].

## 5. Conclusion

GA3 has a dose-dependent toxic effect on the renal cortex of adult male albino rats following 8 weeks of daily exposure. Administration of GA3 at two different doses, 100 ppm (low dose) and 200 ppm (high dose) resulted in histopathological and ultrastructure changes in the renal cortical tissue of male rats. More severe structural changes were detected in the renal cortex of high dose GA3-treated rats. On the other hand, 8 weeks of GA3 withdrawing was insufficient for the complete recovery of these toxic effects.

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