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Efficacy of *Ginkgo biloba* Leaves against Cisplatin Induced Nephrotoxicity in Rats

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ABSTRACT

Nephrotoxicity is one of the most common kidney problems and occurs when the body is exposed to a drug or toxin. The present work aimed to investigate the effect of *Ginkgo biloba* leaves on some minerals utilization in nephrotoxic induced rats. Forty adult male Sprague-Dawley rats (average body weight was 170±10 g) were divided randomly into eight groups as follow: group 1: negative control, was fed on basal diet. Groups 2, 3 and 4 were received *Ginkgo biloba* leaves powder (GBLP) by 1, 2 and 4% levels of diet, respectively. Group 5: positive control, was injected with Cis (7mg/kg body weight) to cause nephrotoxicity in rats. Groups 6, 7 and 8 were treated with GBLP by 1, 2 and 4% levels of diet, respectively and injected with Cis. At the end of the experimental period (6 weeks). The concentration of aspartate aminotransferase (AST), alanine aminotransferase (ALT), serum urea, creatinine levels, serum total proteins, albumin, malondialdehyde (MDA) and glutathione (GSH) were determined. Treatment with GBLP prior to Cis produced protective effects and attenuated these biochemical changes. The protective effects of GBLP were more pronounced for the high level. These results were confirmed by histopathologic observations of the kidney tissues. In conclusion, the beneficial effects of GBLP might be ascribable to its anti-inflammatory and antioxidant properties.

Keywords: kidney Functions, Nephrotoxicity, *Ginkgo biloba* Leaves, Cisplatin, Rats

1. Introduction

Ginkgo biloba (Ginkgo, maidenhair tree) (family: *Ginkgoaceae*; class: *Ginkgoatae*) is one of the oldest living tree species and is considered a “living fossil” (Forman *et al.,* 2022). It’s the only living species in the division Ginkgophyta. The tree is widely cultivated and is native to China. It has various uses in traditional medicine and as a source of food (Olubunmi *et al.,* 2016). It has been prescribed to treat Alzheimer's disease and cognitive deficits. Its biological effects include free radical scavenging, antiapoptotic, anti-inflammatory, and antioxidative activities (Barbalho *et al.,* 2022). In recent years, *Ginkgo biloba* leaves have attracted an increasing attention as a functional food ingredient because they contain numerous bioactive constituents, such as flavonoids, terpenoids, polyphenols, polysaccharides, vitamins, and minerals (Niu *et al.,* 2017).

The kidneys are very important organs that play a role in water electrolyte and acid-base homeostasis. It is responsible for excretion of many toxic metabolic waste products as well as many drugs (Al-Shahed *et al.,* 2020). Kidney diseases are public health problem all over the world (Crews *et al.,* 2019). An exposure to environmental pollutants increased risks of kidney disease. Nephrotoxicity is one of the most common kidney problems and occurs when the body is exposed to a drug or toxin (Barnett and Cummings, 2018). Toxic chemical-induced nephrotoxicity tends to be more common among certain patients and in specific clinical situations. Humans are exposed intentionally and unintentionally to a variety of diverse chemicals that harm the kidney. As drugs, natural products, industrial chemicals, and environmental pollutants that cause nephrotoxicity have increased (Prusty *et al.,* 2012). Nephrotoxicity can be defined as the adverse effect of substances on

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renal function. These substances can include molds and fungi, cancer therapeutics, antibiotics, heavy metals, and drugs of abuse (Barnett and Cummings, 2018).

Cisplatin is still used as a fist-line chemotherapeutic agent for solid tumors such as nasopharyngeal cancer, lung cancer and ovarian cancer (Prasaja *et al.,* 2015). However, cisplatin has severe side effects such as gastrointestinal toxicity, bone marrow suppression, ototoxicity, neuropathy myelosuppression, hepatotoxicity and nephrotoxicity (Al-Malki and Sayed, 2014 and Cagin *et al.,* 2016).

2. Materials and Methods

2.1. Materials

Dried leaves of *Ginkgo biloba* were purchased from Agricultural Research Center, Egypt. Chemicals, casein, cellulose, choline chloride, D-L methionine, vitamin and mineral constituents were purchased from El-Gomhoriya Pharmaceutical Company, Cairo, Egypt. Starch, corn oil, and sucrose were obtained from the Egyptian local market. Cisplatin and chemical kits were obtained from El-Gomhoriya Pharm., Cairo, Egypt. Forty adult male albino rats (Sprague- Dawley strain), weighing about (170±10g) were obtained from the Laboratory Animal Colony, Agricultural Research Center, Giza, Egypt.

2.2. Methods

1. Preparation of *Ginkgo biloba* leaves powder

Dried *Ginkgo biloba* leaves were ground into a fine powder and store in the dark in airtight plastic bags at ambient temperature (21 to 27◦C) and were mixed with basal diet at different tested levels **(Ren *et al.,* 2018)**.

2. Induction of nephrotoxicity in rats

Rats were intraperitoneally injected with a single dose of cisplatin (7 mg/kg) of body weight on fourth day from the beginning of the experiments (Gulec *et al.,* 2006 and Karafakıoğlu *et al.,* 2017).

3. Diet Preparation and Experimental Animal Design:

The basal diet was prepared according to AIN-93M diet (Reeves *et al.,* 1993). Forty adult male albino rats were housed in well conditions in Research Labs, Agricultural Research Center, Giza, Egypt. Rats were adapted for one week on an AIN-93M basal diet. After adaptation period, rats were randomly divided into eight equal groups of 5 rats each. Rats were divided into two main groups, the first one is healthy and the other one suffering from nephrotoxicity. During the experiment period, the quantities of diet, which were consumed and/or waste, were recorded every day. In addition, rat's weight was recorded weekly to determine feed intake, body weight gain and feed efficiency ratio according to Chapman *et al.* (1959).

4. Biochemical Analysis of Serum

At the end of the experimental period (6 weeks), rats were fasted overnight before scarifying and blood samples were collected from each rat and were centrifuged at 3000 rpm for 15 min to obtain the serum for biochemical analysis. Serum aspartate aminotransaminase and alanine aminotransaminase were determined according to the method described by Young, (2001) and alkaline phosphates was determined according to Roy, (1970). serum level of creatinine was determined using the method described by Burtis and Ashwood, (1999) and Young, (2001). Urea in the sample according to method of Tabacco, (1979). Serum total protein concentration was determined using the method described by Burtis and Ashwood (1999). Serum albumin level was determined as described by Young, (1995). Malondialdehyde (MDA) determined according to method of Uchiyana and Mihara (1978). glutathione (GSH) determined according to method of Ellman, (1959).

5. Histopathological examination

Specimens from the kidney were dissected out, washed with normal saline solution to remove blood and placed in 10% neutral buffered formalin for histopathological examination according to

Bancroft and Stevens, (1996). Histopathological examination was done in Veterinary medicine, Cairo University.

6. Statistical Analysis

Results were expressed as the mean standard error ± SE. Data were statistically analyzed for variance "ANOVA" test at P ≤ (0.05) using SPSS statistical software, version 20 was used for these calculations (Armitage and Berry, 1987).

3. Results and Discussion

Results in Table 1 showed that effect of *Ginkgo biloba* leaves powder on initial body weight (BW), final body weight, feed intake (FI), body weight gain (BWG) and feed efficiency ratio (FER) of normal and nephrotoxicity rats. Administration of cisplatin (Cis) to rats significantly (P< 0.05) reduced BWG compared to negative control. These results agreed with those reported by Abdelrahman, *et al.* (2010) and Abdel-Wahab *et al.* (2017) found that significantly (P≤0.05) decreased in body weight in rats receiving cisplatin compared to the control group. GÜNTÜRK *et al.,* 2019 who suggested that Cis-induced weights loss might be due to gastrointestinal side effects and reduced ingestion of food.

Table 1: Effect of *Ginkgo biloba* leaves powder on initial body weight (BW), final body weight, feed intake (FI), body weight gain (BWG) and feed efficiency ratio (FER) of normal and nephrotoxicity rats.

Parameters / Groups	Initial BW	Final BW	FI (g/d/rat)	BWG%	FER
Control (-ve)	175.40±3.73^{a}	228.6±2.61^{a}	**17**	30.40±1.01^{a}	0.114±0.002^{a}
(1% GB)	173.60±1.95^{a}	222.2±1.39^{ab}	**16.5**	28.00±0.39ab	0.104±0.002b
(2% GB)	173.00±2.54^{a}	223.0±2.62ab	**18**	28.92±0.61a	0.100±0.002bc
(4% GB)	172.00±1.30^{a}	221.20±1.91ab	**17.5**	28.62±0.58a	0.100±0.002bc
Control (+ve) Cis	176.20±2.15^{a}	200.1±2.62c	**12.5**	9.20±0.31f	0.048±0.003d
(1% GB)	175.20±1.65^{a}	211.0±1.35b	**13.5**	20.90±0.60d	0.096±0.002c
(2% GB)	171.80±2.92^{a}	213.6±2.81b	**15**	24.31±0.48c	0.100±0.001bc
(4% GB)	173.60±3.61^{a}	217.20±1.75ab	**15.5**	25.20±0.69bc	0.100±0.002bc

*Mean values are expressed as means ± SE.
*Mean values at the same column with the same superscript letters are not statistically significant at P<0.05.
* **(GB):** *Ginkgo biloba.* * **Cis:** Cisplatin.

Data demonstrate that normal rats in the three levels 1, 2 and 4%, received *Ginkgo biloba* leaves powder showed no significant change (P<0.05) in BWG compared to negative control. These results were in the same line with the results of Ren *et al.,* (2018) provided evidence that body weight was not significantly affected by the addition of Ginkgo leaves (GL) and extract *Ginkgo biloba* (EGB) in diets. Hu, (2020) reported that Ginkgo leaves had no significant effect on the average daily feed intake, final body weight, and average daily gain. On the other hand, (Banin *et al.,* 2014) and (Hirata *et al.,* 2015) demonstrated that GbE treatment significantly reduced food intake and body adiposity while it protected against hyperglycemia and dyslipidemia in diet-induced obesity rats.

Results recorded in Table 1 illustrated that *Ginkgo biloba* leaves powder administrated to nephrotoxicity rats a significant (P<0.05) increase in BWG in the three levels 1,2 and 4%, compared to nephrotoxicity control group. The obtained findings agreed with Khattab, (2012) concerning the effect of *Ginkgo biloba* extract (GbE) on rats, the ingestion showed slightly increase in weight gain percent, food intake and FER, there were no significant difference as compared with control group. Pretreatment of rats with GbE showed a significant increase in weight gain percent (p<0.001), food intake (p<0.001) and FER (p<0.01) as compared with nephrotoxicity group.

Ginkgo biloba leaves, the dried leaves of *Ginkgo biloba*, contain flavonoids, terpene lactones, polyphenols, polysaccharides, and other compositions with a variety of biological functions, such as

improving growth performance, nutrient digestibility, and antioxidant activities of animals as found in the present study that supported by (Niu *et al.,* 2017).

In conclusion, the results of the present study indicated that feed intake and body weight gain was not affected by the addition of *Ginkgo biloba* leaves in diets. Whereas *Ginkgo biloba* leaves were improved body weight gain and feed efficiency ratio to nephrotoxicity rats.

Data presented in Table 2 revealed that serum concentration of aspartate aminotransferase (AST) and alanine aminotransferase (ALT) significantly increased (*P<0.05*) in nephrotoxicity control group when compared to negative control group. The obtained results were in harmony with several research that revealed (Bhalchandra and Alqadhi, 2018 and Elkomy *et al.,* 2020) who have injection of cisplatin significantly ($P \leq 0.05$) increased serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST). Taghizadeh *et al.,* (2021) mentioned that cisplatin treated mice showed a significant increase in serum AST and ALT levels compared with the control group ($p < .0001$). A similar result was also observed by Gong *et al.* (2021) confirmed that cisplatin treatment significantly increased ALT and AST levels in plasma.

Table 2: Effect of *Ginkgo biloba* leaves powder on serum aspartate aminotransferase (AST), alanine aminotransferase (ALT) of normal and nephrotoxicity rats.

Groups \ Parameters	AST	ALT
	(µ /L)	
Control (-ve)	19.20±0.66^{f}	6.22±0.20^{d}
(1% GB)	21.60±0.74^{e}	6.94±0.53^{d}
(2% GB)	20.20±0.58^{ef}	6.20±0.35^{d}
(4% GB)	20.00±0.89^{ef}	6.16±0.27^{d}
Control (+ve) Cis	40.20±0.80^{a}	25.58±0.85^{a}
(1% GB)	34.21±0.37^{b}	19.25±0.42^{b}
(2% GB)	30.00±0.70^{c}	16.90±0.30^{bc}
(4% GB)	26.45±0.58^{d}	15.12±0.48^{c}

*Mean values are expressed as means ± SE.
*Mean values at the same column with the same superscript letters are not statistically significant at P<0.05.
* **(GB):** *Ginkgo biloba*. * **Cis:** Cisplatin.

In the same table results show *Ginkgo biloba* leaves powder administrated to normal rats increased AST in the three levels 1,2 and 4%, there are significantly increased (*P<0.05*) in 1% level whereas the two levels 2 and 4% showed no significant when compared to negative control group, also this result showed that serum concentration of ALT in the three levels 1,2 and 4% was no significant when compared to negative control group. This was in congruence with the findings reported by Cxavusxog˘lu *et al.,* (2011) show that there are no significant differences in the levels of AST and ALT among the control and the groups treated with *G. biloba* alone ($P > .05$). Similar to the result of Agarwal *et al.,* (2018) concluded that when levels of markers of liver function (activities of ALT and AST) in Ginkgo consumers were compared to non-consumers, the differences were not statistically significant ($P > 0.01$). These data indicate moderate Ginkgo intake of consumers does not alter liver function.

Table 2 also shows that *Ginkgo biloba* leaves powder administrated to nephrotoxicity rats decreased serum concentration of AST and ALT in the three levels 1,2 and 4% was significant decrease (*P<0.05*) when compared to nephrotoxicity control group. Results of liver enzymes were similar to that obtained by Cha´vez-Morales *et al.,* (2010) noted that *Ginkgo biloba* extract (GbE) lowers the high serum activity of AST and ALT produced by carbon tetrachloride (CCl4) group. In another study by Khattab, (2012) Administration of GbE to rats showed nonsignificant changes in serum liver enzyme activities as compared to control group. Pretreatment of rats with GbE caused a marked protection evidenced by significant reduction ($p<0.001$) in serum AST and ALT enzyme activities.

Results of our study concluded that *Ginkgo biloba* leaves powder showed nonsignificant changes in serum liver enzyme activities as compared to negative control group, although there were lowers the high serum activity of AST and ALT produced by cisplatin treatment group.

Results in Table 3 show the effect of *Ginkgo biloba* leaves powder on creatinine, urea, total protein and albumin of normal and nephrotoxicity rats. Data revealed that cisplatin administration resulted in nephrotoxicity as indicted by significant ($P < 0.05$) elevation in the levels of serum creatinine and urea, while serum total protein and albumin concentrations significantly ($P \leq 0.05$) decreased as compared with negative control group. These results are in accordance with previous studies which have demonstrated that (Brahmi *et al.,* 2012) and (Maheshwari *et al.,* 2013) Cis significantly increased the levels of urea and creatinine and decreased the levels of albumin and total protein. In the same line a study by (Elkomy *et al.,* 2020) who found that injection of cisplatin significantly ($P \leq 0.05$) increased creatinine and urea levels, while serum total protein and albumin concentrations significantly ($P \leq 0.05$) decreased.

Table 3: Effect of *Ginkgo biloba* leaves powder on creatinine, urea, total protein and albumin of normal and nephrotoxicity rats.

Parameters / Groups	Creatinine mg/dl	Urea mg/dl	Total Protein mg/dl	Albumin mg/dl
Control (-ve)	0.72±0.01c	48.76±0.44d	6.85±0.56a	3.33±0.15a
(1% GB)	0.86±0.02bc	50.03±0.50d	6.80±0.81a	3.31±0.12a
(2% GB)	0.85±0.01bc	49.53±0.30d	6.70±0.29a	3.15±0.24a
(4% GB)	0.79±0.01bc	47.93±0.26d	6.85±0.22a	3.14±0.25a
Control (+ve) Cis	2.15±0.17a	71.79±0.55a	4.14±0.11c	2.10±0.23c
(1% GB)	2.11±0.11a	70.76±0.93ab	4.20±0.21c	2.34±0.14c
(2% GB)	1.93±0.08a	69.35±0.66b	4.58±0.16c	2.43±0.34bc
(4% GB)	0.99±0.03b	54.83±0.52c	5.61±0.16b	2.56±0.23b

*Mean values are expressed as means ± SE.
*Mean values at the same column with the same superscript letters are not statistically significant at P<0.05.
* **(GB):** *Ginkgo biloba*. * **Cis:** Cisplatin.

The impairment of kidney function by Cis was previously reported by many researchers (Shimeda *et al.,* 2005 and Palipoch *et al.,* 2014 and Dwivedi *et al.,* 2017). It was suggested that Cis causes alterations in glomerular function. Cis induces mesangial cells contraction, alters the filtration surface area and modifies the ultrafiltration coefficient factors that decrease the glomerular filtration rate (Aydogan, 2008).

Table 3 also shows that the effect of *Ginkgo biloba* leaves powder on creatinine, urea, total protein and albumin of normal rats was no significant when compared to negative control group.

Results in the same table also show *Ginkgo biloba* leaves powder administrated to nephrotoxicity rats on creatinine, urea, total protein and albumin of normal rats was no significant in the two levels 1 and 2%, when compared with nephrotoxicity control group. While, *Ginkgo biloba* leaves powder administrated to nephrotoxicity rats decreased serum creatinine and urea, while serum total protein and albumin concentrations significantly ($P \leq 0.05$) increased in the level 4%, when compared to nephrotoxicity control group. Our results appear to be similar to those reported by (Elatrash and Abd El-Haleim, 2015) indicate that serum total protein, and albumin were significantly increased in the serum, while serum urea and serum creatinine were significantly decrease after administration of *Ginkgo biloba*. In a study by Okuyan *et al.,* (2012) revealed that *Ginkgo biloba* extract significantly decreased the serum creatinine, which had increased as a result of cisplatin administration.

Results of Table 3 concluded that *Ginkgo biloba* leaves powder did not show any significant difference in the normal group when compared with negative control group. These data suggest that supplementation of *Ginkgo biloba* leaves powder may be helpful to reduce cisplatin nephrotoxicity for the high level.

Results in Table 4 show effect of *Ginkgo biloba* leaves powder on malondialdehyde (MDA) and glutathione (GSH)of normal and nephrotoxicity rats. Data revealed that MDA was significantly increased (*P<0.05*) in nephrotoxicity control group when compared to negative control group, whereas the GSH was significantly decreased (*P<0.05*). These results were in agreement with Taghizadeh *et al.,* (2021) revealed that cisplatin increased oxidative stress (increased MDA and reduced GSH).

Results in the same Table 4 also show *Ginkgo biloba* leaves powder administrated to normal rats of MDA and GSH in the three levels 1,2 and 4%, were no significant when compared to negative control group. In the level 4%, the value of GSH near to normal rat comparing with the two levels 1 and 2% groups.

Table 4: Effect of *Ginkgo biloba* leaves powder on malondialdehyde (MDA) and glutathione (GSH) of normal and nephrotoxicity rats.

Parameters Groups	MDA (u/ml)	GSH (m mol/ml)
Control (-ve)	2.57±0.12d	4.91±0.05ab
(1% GB)	2.35±0.07d	4.85±0.12b
(2% GB)	2.06±0.05d	4.81±0.21b
(4% GB)	1.097±0.10d	4.96±0.17ab
Control (+ve) Cis	13.62±0.50a	2.92±0.07c
(1% GB)	11.75±0.26b	4.31±0.09b
(2% GB)	10.37±0.29c	4.84±0.14b
(4% GB)	9.31±0.13c	5.56±0.22a

*Mean values are expressed as means ± SE.
*Mean values at the same column with the same superscript letters are not statistically significant at P<0.05.
* **(GB):** *Ginkgo biloba.* * **Cis:** Cisplatin.

Results recorded in Table 4 illustrated that *Ginkgo biloba* leaves powder administrated to nephrotoxicity rats decreased serum concentration of MDA in the three levels 1,2 and 4% was significant decrease (*P<0.05*) when compared to nephrotoxicity control group, whereas the GSH was significantly increased (*P<0.05*) in the three levels 1,2 and 4%. These results were similar to that obtained by Ahmed *et al.,* (2006) who reported that the level of MDA content in positive control group was significantly increased under oxidative stress. But in the various groups treated with *Ginkgo biloba* extracts there was significant decrease in the levels of MDA content. In the same line, Khattab, (2012) results showed that, the level of MDA in the rats' liver tissue, significantly elevated (p<0.001) in CCl4 intoxicated group compared to control group. On the other hand, pretreatment of rats with GbE revealed amelioration in hepatic MDA content, since the value of MDA showed significantly reduced (p<0.001) as compared to CCl4 group. Regarding, hepatic GSH, the results revealed significant reduction (p<0.001) in rats intoxicated with CCl4 as compared to control group. Pretreatment of rats with GbE markedly preserved hepatic GSH, the value of GSH near to normal levels comparing with CCl4 group. Bing and Zhaobao, (2010) who found that *Ginkgo biloba* extract can help to increase the activity of the antioxidant enzymes in liver tissue, reduce the lipid peroxidation injury in liver tissue.

In conclusion, our results revealed that the *Ginkgo biloba* leaves powder does not alter MDA and GSH in normal rats, whereas the *Ginkgo biloba* leaves powder reduced MDA and increased GSH in cisplatin treatment group when compared to nephrotoxicity control group.

3.1. Histopathological examination of kidneys

Microscopically, Kidney's section of negative control group revealed the normal histological structure of renal parenchyma (normal renal cortex and renal medulla) (Photos 1 and 2). Kidney's section of rats supplemented with 1% of *Ginkgo biloba* leaves powder exhibited no histopathological alterations (Photos 3 and 4). Moreover, some sections from rats supplemented with 2% of *Ginkgo biloba* leaves powder showed no histopathological alterations (Photos 5 and 6). Furthermore, kidneys of rats supplemented with 1% of *Ginkgo biloba* leaves powder revealed no histopathological alterations (Photos 7 and 8).

On the other hand, kidney sections of positive control group indicated marked vacuolar degeneration of epithelial lining renal tubules (Photo 9), intratubular inflammatory cells infiltration (Photo 10), thickening of the parietal layer of Bowman's capsule and basement membrane of renal tubules as well as interstitial inflammatory cells infiltration (Photo 11). Meanwhile, kidney sections of rats treated with 1% of *Ginkgo biloba* leaves powder + Cis described vacuolar degeneration of epithelial lining some renal tubules (Photo 12) and focal necrosis of renal tubules associated with inflammatory cells infiltration (Photo 13), and eosinophilic proteinaceous cast in the lumen of renal tubules (Photo 14). However, some examined sections from group treated with 2% of *Ginkgo biloba* leaves powder + Cis found vacuolar degeneration of epithelial lining some renal tubules and endothelial lining glomerular tuft (Photo 15), Moreover, some sections from group treated with 2% of *Ginkgo biloba* leaves powder + Cis showed vacuolar degeneration of endothelial lining glomerular tuft (Photo 16), whereas, other sections revealed no histopathological alterations (Photo 17). On the other hand, some sections from group treated with 4% of *Ginkgo biloba* leaves powder + Cis described no histopathological alterations (Photos 18, 19 and 20).

Results of the histological examination of previous studies demonstrated changes in kidney structure due to Cis treatment. In several studies, the pathological mechanisms of cisplatin-induced nephrotoxicity mainly manifest as decreases in renal blood flow and glomerular filtration rate and ischemia or necrosis of proximal renal tubular epithelial cells (Cagin *et al.,* 2015; Wang *et al.,* 2019 and Fang *et al.,* 2021).

In this study, pretreatment with *Ginkgo biloba* leaves powder reduced the severity of renal histological alterations induced by Cis. Our results are consistant with previous reports of Song *et al.,* (2013) who suggested that less histological damage was observed in renal tubules in EGb group. In addition, our results appear to be similar to those reported by Fattiny and Al-Amri, (2019) and Kareem *et al.,* (2022) who concluded that *Ginkgo biloba* was effective in attenuating the level of inflammation by decreasing the exudate, granuloma, and inflammatory markers. The underlying mechanisms could be the inhibitory effect on the expression of the inflammatory cytokines and endothelial adhesion molecule.

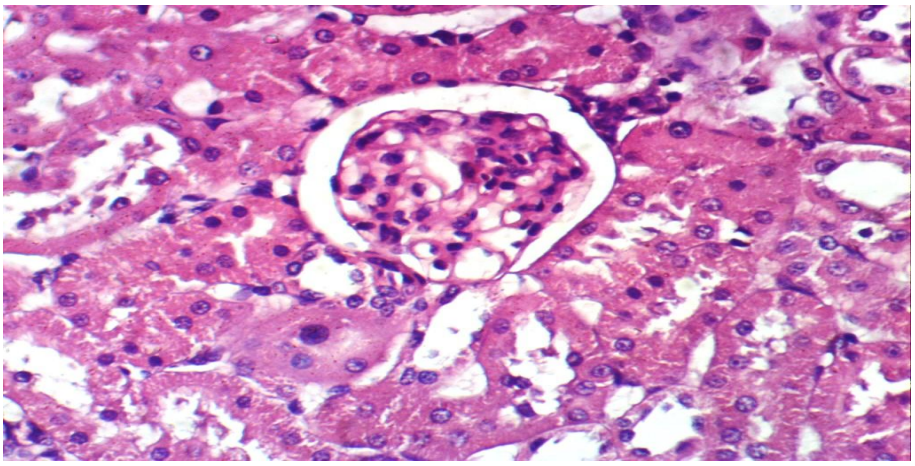

Photo 1: A photomicrograph of a kidney section of negative control group showed normal histological structure (H & E × 400).

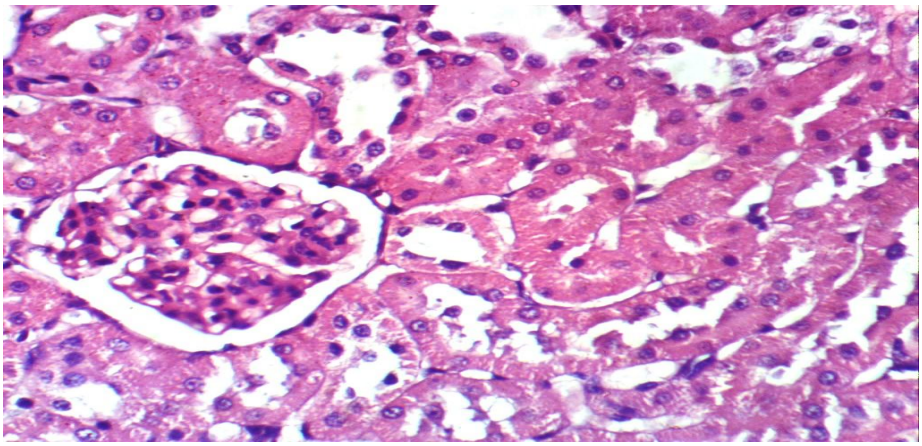

Photo 2: A photomicrograph of a kidney section of negative control group showed normal histological structure (H & E × 400).

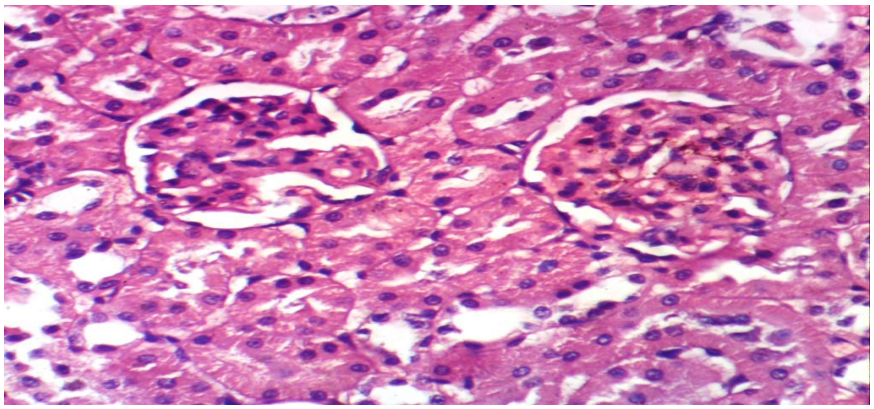

Photo 3: A photomicrograph of a kidney section of rats supplemented with 1% of *Ginkgo biloba* leaves powder showed no histopathological alterations (H & E X 400).

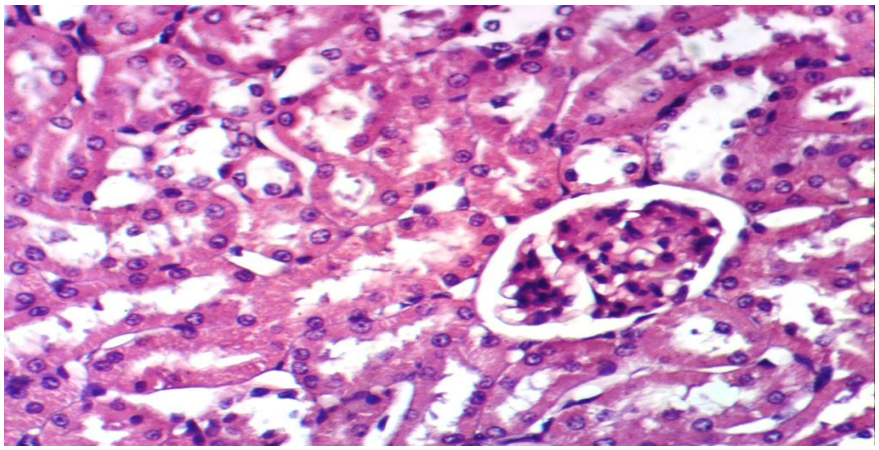

Photo 4: A photomicrograph of a kidney section of rats supplemented with 1% of *Ginkgo biloba* leaves powder showed no histopathological alterations (H & E X 400).

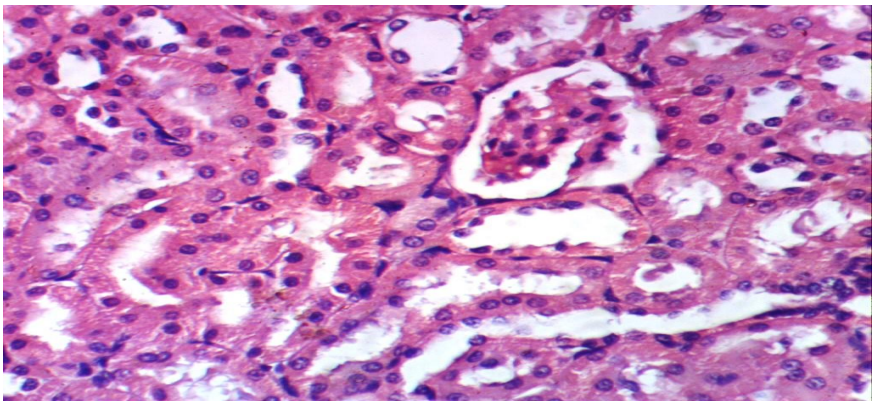

Photo 5: A photomicrograph of a kidney section of rats supplemented with 2% of *Ginkgo biloba* leaves powder showed no histopathological alterations (H & E X 400).

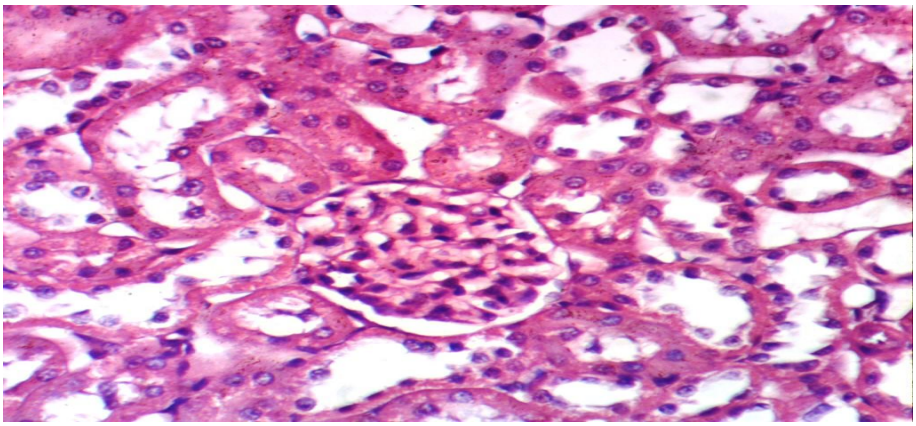

Photo 6: A photomicrograph of a kidney section of rats supplemented with 2% of *Ginkgo biloba* leaves powder showed no histopathological alterations (H & E X 400).

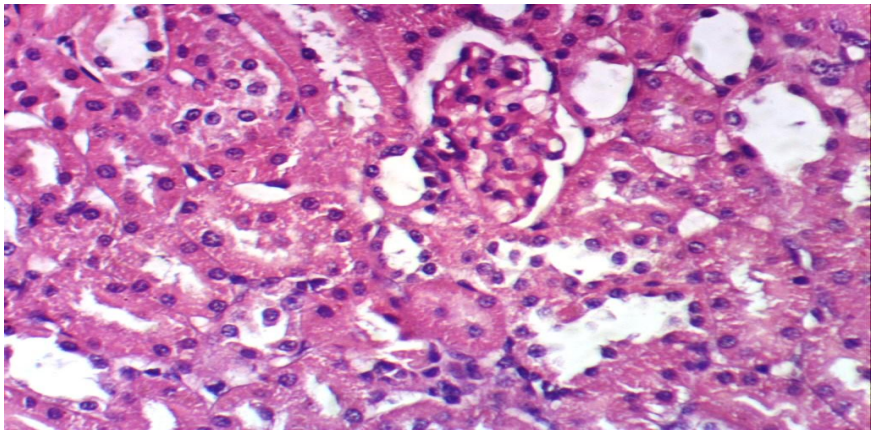

Photo 7: A photomicrograph of a kidney section of rats supplemented with 4% of *Ginkgo biloba* leaves powder showed no histopathological alterations (H & E X 400).

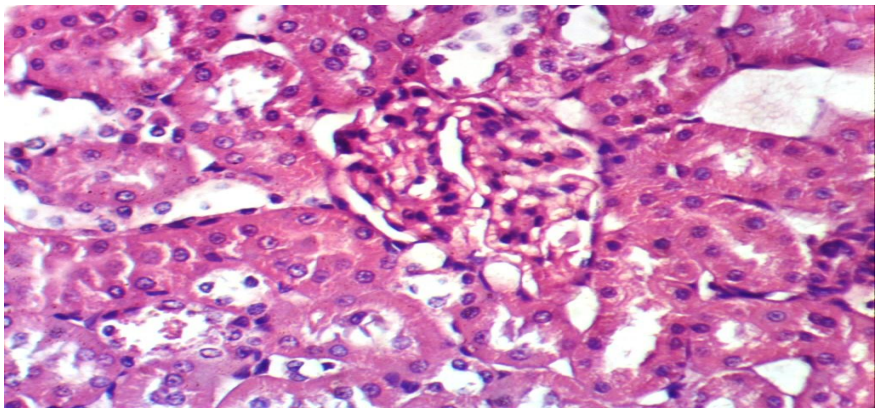

Photo 8: A photomicrograph of a kidney section of rats supplemented with 4% of *Ginkgo biloba* leaves powder showed no histopathological alterations (H & E X 400).

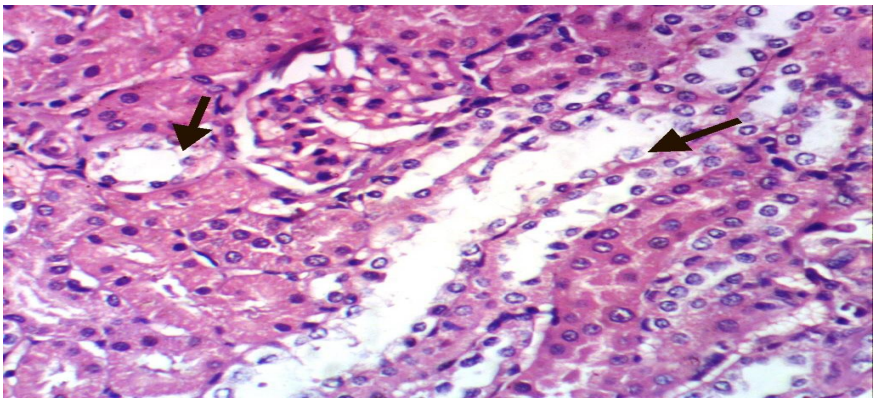

Photo 9: A photomicrograph of a kidney section of positive control showed marked vacuolar degeneration of epithelial lining renal tubules (H & E X 400).

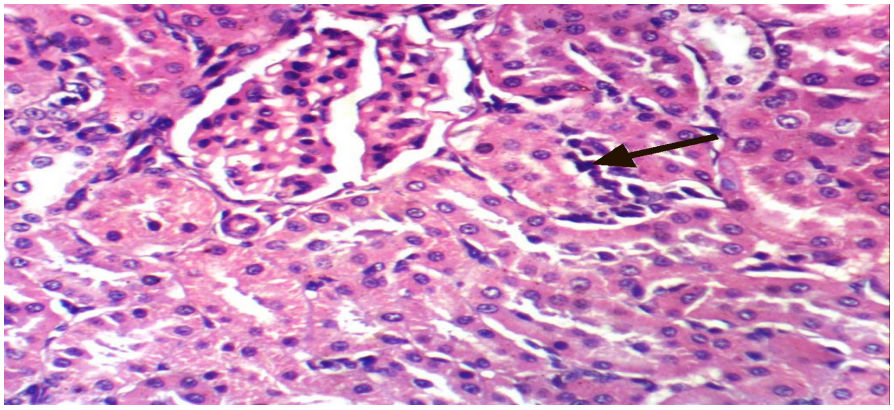

Photo 10: A photomicrograph of a kidney section of positive control showed intratubular inflammatory cells infiltration (H & E X 400).

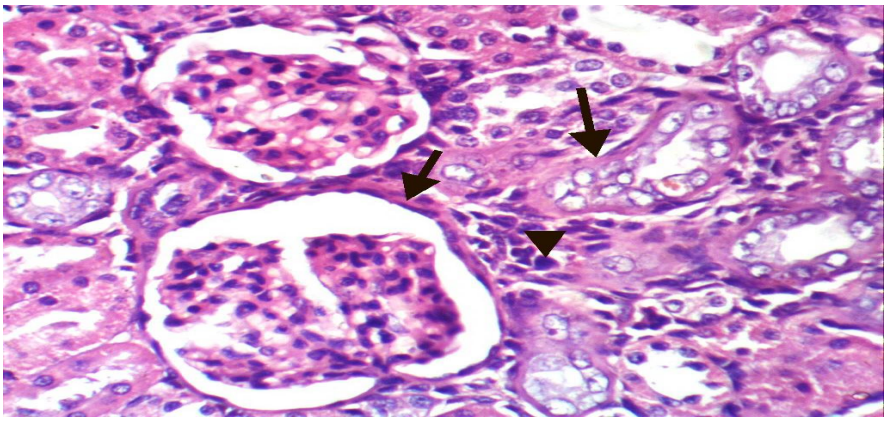

Photo 11: A photomicrograph of a kidney section of positive control showed thickening of the parietal layer of Bowman's capsule and basement membrane of renal tubules as well as interstitial inflammatory cells infiltration (H & E X 400).

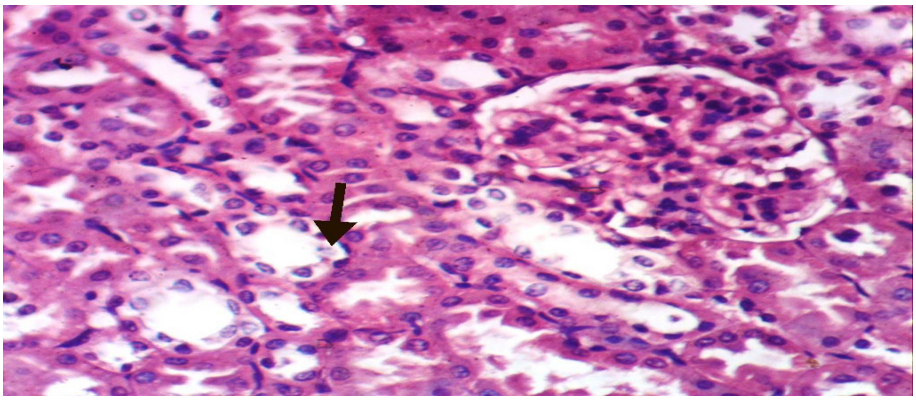

Photo 12: A photomicrograph of a kidney section of positive control showed vacuolar degeneration of epithelial lining some renal tubules (H & E X 400).

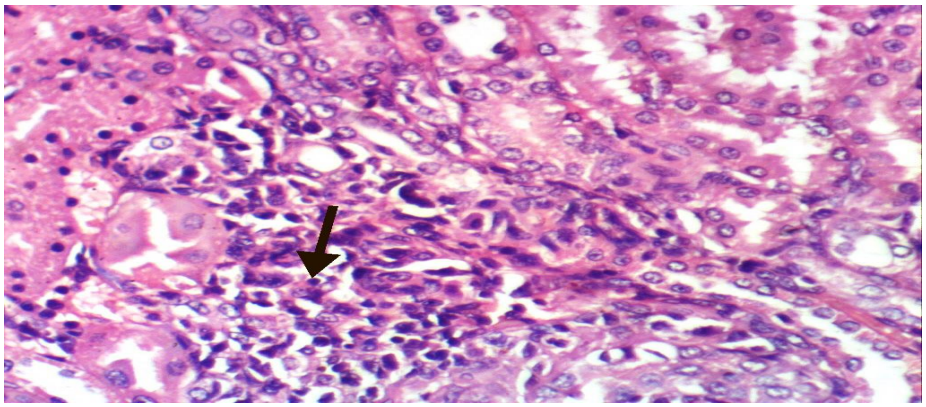

Photo 13: A photomicrograph of a kidney section of rats treated with 1% of *Ginkgo biloba* leaves powder + Cis showed focal necrosis of renal tubules associated with inflammatory cells infiltration (H & E X 400).

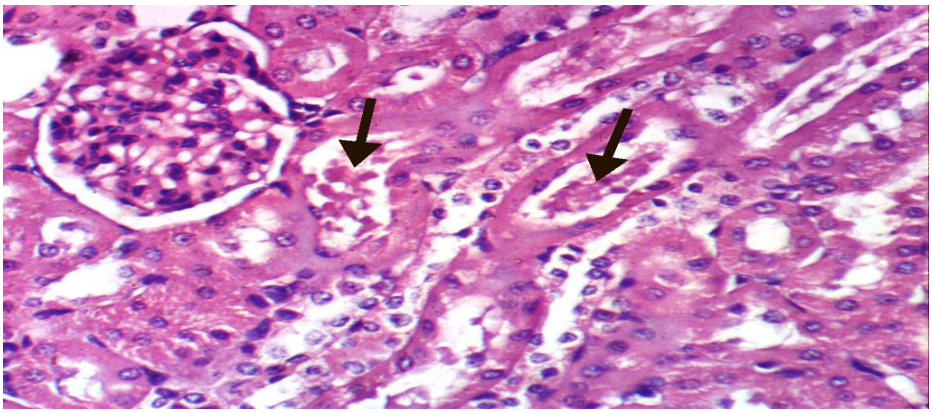

Photo 14: A photomicrograph of a kidney section of rats treated with 1% of *Ginkgo biloba* leaves powder + Cis showed eosinophilic proteinaceous cast in the lumen of renal tubules (H & E X 400).

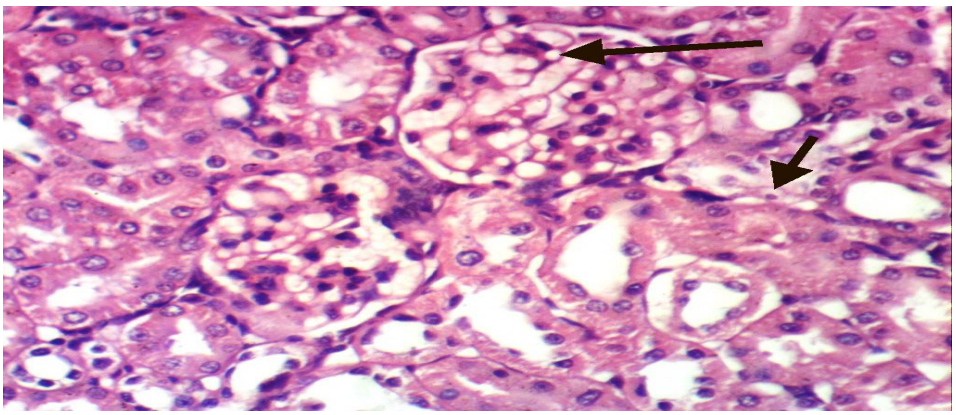

Photo 15: A photomicrograph of a kidney section of rats treated with 2% of *Ginkgo biloba* leaves powder + Cis showed vacuolar degeneration of epithelial lining some renal tubules and endothelial lining glomerular tuft (H & E X 400).

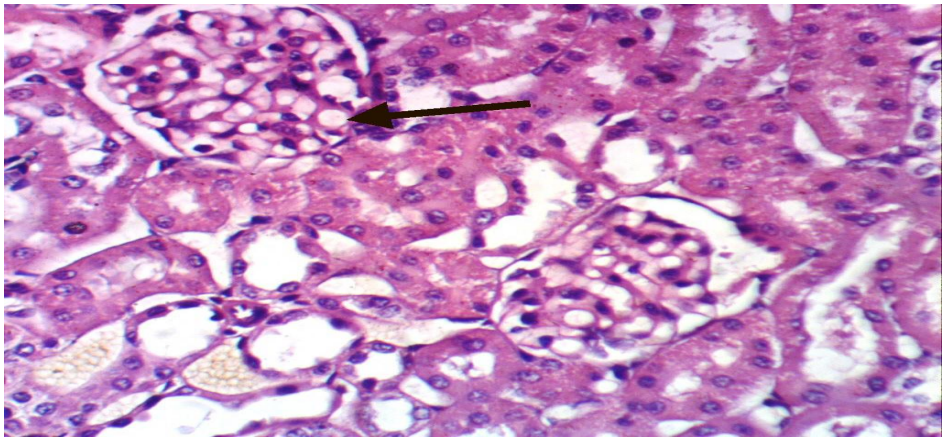

Photo 16: A photomicrograph of a kidney section of rats treated with 2% of *Ginkgo biloba* leaves powder + Cis showed vacuolar degeneration of endothelial lining glomerular tuft (H & E X 400).

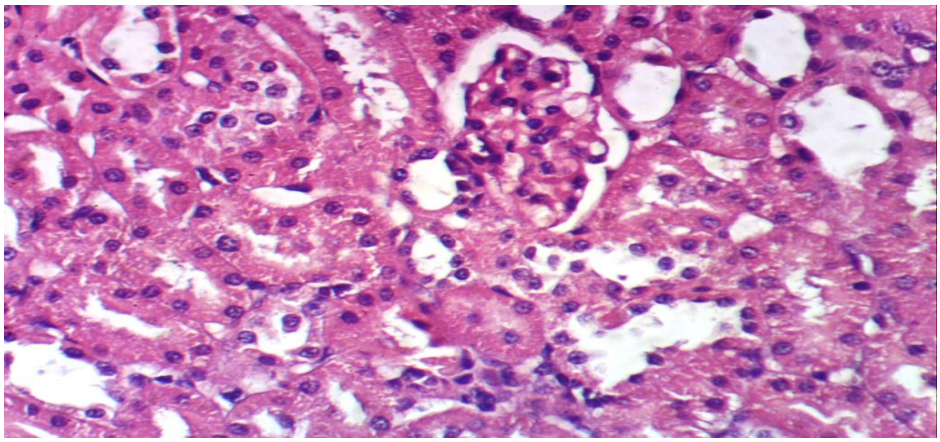

Photo 17: A photomicrograph of a kidney section of rats treated with 2% of *Ginkgo biloba* leaves powder + Cis showed no histopathological alterations (H & E X 400).

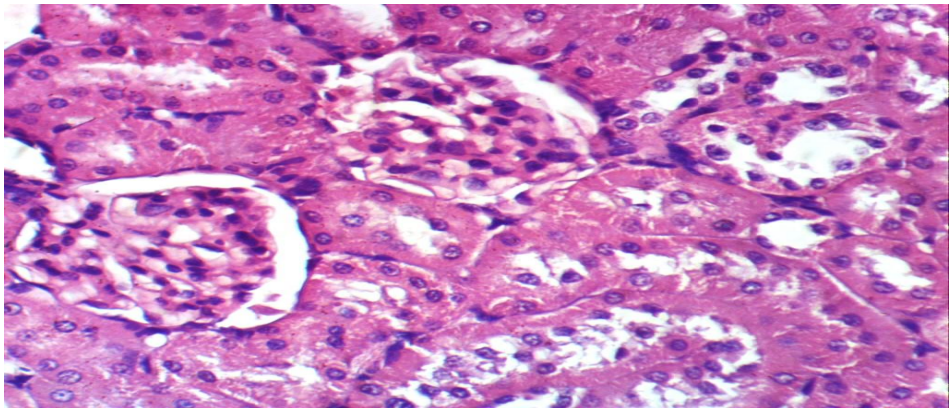

Photo 18: A photomicrograph of a kidney section of rats treated with 4% of *Ginkgo biloba* leaves powder + Cis showed no histopathological alterations (H & E X 400).

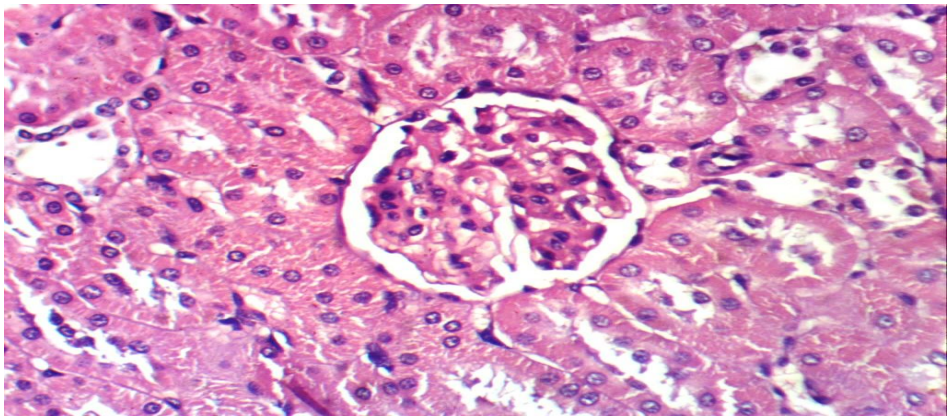

Photo 19: A photomicrograph of a kidney section of rats treated with 4% of *Ginkgo biloba* leaves powder + Cis showed no histopathological alterations (H & E X 400).

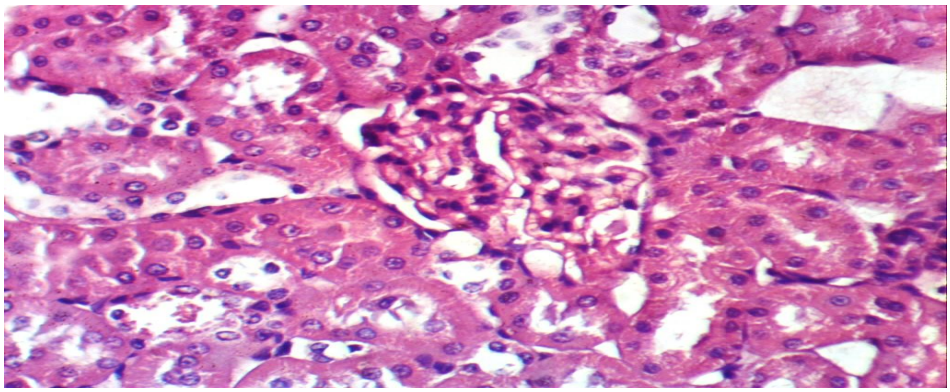

Photo 20: A photomicrograph of a kidney section of rats treated with 4% of *Ginkgo biloba* leaves powder + Cis showed no histopathological alterations (H & E X 400).

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