Original Article

Effect of Supplemented Diet with Ginkgo Biloba Leaves Powder on Some Biochemical Parameters and Minerals Content in Cisplatin-Induced Nephrotoxicity in Rats

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Abstract

Nephrotoxicity is one of the most common kidney problems which occurs when the body is exposed to toxic drugs or toxins. The present work aimed to investigate the effect of Ginkgo biloba leaves powder (GBLP) on some biochemical parameters and minerals content in Cisplatin (Cis)-induced nephrotoxic rat model. Forty adult male Sprague-Dawley rats (body weight 170±10 g) were randomly divided into eight groups, of 5 rats each. Group 1 negative control: was fed on the basal diet only. Groups 2, 3 and 4 were fed on basal diet mixed with GBLP at 1, 2 and 4% concentrations, respectively. Group 5: positive control: was intraperitoneally injected with a single dose of Cis at 7 mg/kg b. wt. to induced nephrotoxicity in rats. Groups 6, 7 and 8 were fed on basal diet mixed with GBLP at 1, 2 and 4% levels, respectively and injected with Cis as mentioned before. At the end of the experimental period (6 weeks), the levels of aspartate aminotransferase (AST), alanine aminotransferase (ALT), blood urea, creatinine, total proteins, albumin, malondialdehyde (MDA), glutathione (GSH) and minerals contents were determined. In addition, the effect of feeding GBLP on formalin-induced local inflammation in the paw's thickness was measured at different periods. Diet supplementation with GBLP improved the above mention biochemical parametrs at 2 and 4%. Feeding on GBLP prior to Cis injection produced protective effects and returned the biochemical parameters to nearly normal levels. The protective effect of GBLP was more pronounced at the high level (4%). In conclusion, the beneficial effects of GBLP may be ascribed to its hepatoprotective, renoprotective, antioxidant and anti-inflammatory properties and high levels of minerals content.

Keywords: Ginkgo biloba leaves, Nephrotoxicity, Biochemical parametrs, Minerals, Acute pedal inflammation

INTRODUCTION

Ginkgo biloba (Ginkgo, Maidenhair tree) (Family *Ginkgoaceae*) is one of the oldest living tree species and is considered as a living fossil **(Forman *et al.*, 2022)**. It is the only living species in 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)**. Ginkgo biloba has been prescribed to treat Alzheimer's disease and cognitive deficits. It has biological effects such as free radical scavenging, antiapoptotic, anti-inflammatory, and antioxidant 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, as flavonoids, terpenoids, polyphenols, polysaccharides, vitamins, and minerals **(Niu *et al.*, 2017)**.

The kidney is very important organ that plays an important role in water and electrolyte and balance of acid-base. 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 allover the world **(Crews *et al.*, 2019)**. An exposure to environmental pollutants increased risks to kidney disease. Nephrotoxicity is one of the most common kidney problems that occurs when the body is exposed to drugs or toxins **(Barnett and Cummings, 2018)**. Toxic chemical-induced nephrotoxicity tends to be more common among certain patients in 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 to be increased **(Prusty *et al.*, 2012)**. Nephrotoxicity can be defined as the adverse effect of toxic substances on renal function. These substances can include molds and fungi, cancer therapeutics, antibiotics, heavy metals **(Barnett and Cummings, 2018)**.

Inflammation is a body's natural response against harmful pathogen and chemical stimuli that occurs in two stages namely, acute and chronic inflammation. Acute inflammation is a part of innate immunity initiated by the immune cells that persist only for a short time. However, if the inflammation continued, the second stage of inflammation called chronic inflammation **(Ajaikumar *et al.*, 2018)**. Inflammation, a process intimately linked to renal disease, can be defined as a

complex network of interactions between renal parenchymal cells and body immune cells **(Andrade-Oliveira *et al.*, 2019)**.

Materials and Methods

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 a local market. Cisplatin and biochemical kits were obtained from El-Gomhoriya Pharmaceutical Company, Cairo, Egypt. Forty adult male albino rats of Sprague-Dawley strain weighing 170±10g were obtained from the Laboratory Animal Colony, Agricultural Research Center, Giza, Egypt.

Methods

Preparation of Ginkgo biloba leaves powder

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

Chemical analysis of Ginkgo biloba leaves powder

Chemical composition of minerals (calcium, sodium, potassium, zinc, iron, and copper) was determined according to **A.O.A.C., (2012)** and **Lee *et al*., (2019)** and conducted at Food Safety and Quality Control Laboratory, Faculty of Agriculture, Cairo University, Egypt.

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)**.

Preparation of diet and experimental 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 Laboratory, 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 second suffered 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)**.

Biochemical analysis

At the end of 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 clear serum for biochemical analysis. Serum aspartate aminotransaminase and alanine aminotransaminase were determined according to the method described by **Young, (2001**). Serum level of creatinine was determined using the method described by **Burtis and Ashwood, (1999)** and **Young, (2001)**. Urea levels were determined 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 estimated as described by **Young, (1995)**. Serum mineral contents of calcium, sodium, potassium zinc, iron, and copper determined according to **Gosling, (1986)**. Malondialdehyde (MDA) determined according to method of **Uchiyana and Mihara (1978)**. Glutathione (GSH) was determined according to method of **Ellman, (1959)**.

Anti-inflammatory assessment

At the last week of the feeding with Ginkgo biloba leaves powder, three rats were selected from each of group and right paws were injected by 0.1ml of 4% formalin in skin of the paw. After 2, 4 and 6 hours the thickness of the paw was measured using skin caliber. The anti- inflammatory effect was assessed by reduction in thickness of rats' paws.

Statistical Analysis

Results were expressed as means ±standard error (SE). Data were statistically analyzed using analysis of variance "ANOVA" test at $P \leq (0.05)$. SPSS statistical software, version 20 was used for these calculations **(Armitage and Berry, 1987).**

Results and Discussion

Chemical composition of ginkgo biloba leaves powder was recorded in **Table 1**. The data indicated that calcium, potassium, iron, sodium, copper, iron, and zinc at 1990.25, 1157, 37.36, 375.82, 0.552 and 0.768 mg/100g, respectively. Results of chemical composition were nearly similar to that reported by **Gafurdjanov *et al*., (2021)** demonstrated that Ginkgo biloba leaves contain important macro-and micronutrients such as calcium, potassium, iron, sodium, copper and zinc, which are necessary for the vital activity of the human body and normal metabolism. The most common elements in the leaves of ginkgo are calcium (1391.29 – 2557.73) mg/100g. The amount of potassium in the leaves of ginkgo was

(749.15 – 1156.23) mg/100g. Iron was found to be abundant in the leaves of ginkgo (37.30 – 65.51) mg/100g. The amount of sodium in the leaves of ginkgo was (50.41- 51.53) mg/100g. The amount of copper in the leaves of ginkgo was (0.566 – 0.583) mg/100g. The amount of zinc in green leaves was (0.863 mg/l – 1.686) mg/l00g. In the same line a study by **(Nwosu *et al*., 2018)** provided evidence that the results of mineral analyses on whole ginkgo biloba dried leaves showed that high concentrations in macro minerals especially calcium and magnesium and followed by phosphorous, potassium, sodium, iron, zinc, manganese, copper and selenium.

Results in **Table 2** 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 a significant ($P\leq0.05$) decrease in body weight of rats received Cisplatin as compared to the control group. **Güntürk *et al*., 2019** suggested that Cisplatin-induced weights loss might be due to gastrointestinal side effects and reduced ingestion of food. 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 2** 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.

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 to the basal diet. Whereas Ginkgo biloba leaves powder improved body weight gain and feed efficiency ratio (FER) in nephrotoxic rats.

Data presented in **Table 3** 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 ALT and AST. **Taghizadeh *et al*., (2021)** mentioned that Cisplatin treated mice showed a significant increase in serum AST and ALT levels as compared to 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. 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 **Cxavusxoglu *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 as 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 3** 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 a*l., (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 4** 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. 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 4** 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 4** 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 5** 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 5** 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. Results recorded in **Table 5** 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 Ginkgo biloba leaves powder reduced MDA and increased GSH in Cisplatin treatment group as compared to nephrotoxic positive control group.

As shown in **Table 6** effect of ginkgo biloba leaves powder on formalin-induced inflammation for different times on the paw's thickness of normal and nephrotoxic rats. The obtained results showed that paw's thickness was significantly increased ($P<0.05$) in nephrotoxicity control group when compared to negative control group, 2, 4 and 6hrs post administration. In a study by **(Amirshahrokhi and Khalili, 2015)** who suggested that inflammatory mechanisms have a significant role in the pathogenesis of Cisplatin-induced nephrotoxicity. **Table 6** also showed that there were no significant differences in paw's thickness in 1% level group of normal rats compared to negative control group, 2, 4 and 6hrs post administration. While, there was a significant decrease in paw's thickness of normal rats given ginkgo biloba leaves powder in the levels 2 and 4% as compared to negative control group, 4 and 6hrs post administration. The results were similar to the findings of **(Zhou *et al.*, 2014)** who demonstrated that extract of Ginkgo biloba leaves possesses several clinical beneficial effects such as anti-inflammatory property. **Okhti *et al.*, (2021)** G. biloba shows an activity against inflammation. **(Abdel-Emama and Abd-Eldayem, (2022)** who found that the ginkgo biloba extract effectively reduced swelling in the paw swelling. Data presented in **Table 6** results revealed that there were no significant differences in paw's thickness in 1 and 2% levels group of nephrotoxicity rats, 2 and 4hrs post administration as compared to positive nephrotoxicity rats. However, there was a significant decrease in paw's thickness between nephrotoxicity rats in 1 and 2% levels group and positive nephrotoxicity rats, 6hrs post administration. Results of the same table show that there was a significant decrease in paw's thickness between nephrotoxicity rats in 4% level group and positive nephrotoxicity rats, 2, 4 and 6hrs post administration. These results were similar to that obtained by **Abdel-Salam *et al.*, (2004)** who reported

that ginkgo biloba extract (GbE) was assessed in models of acute inflammation induced by formalin in the rat, GbE was also significant inhibition of formalin-induced paw oedema. Results suggest that GbE may be of clinical value as an anti-inflammatory. **Song *et al*., (2013)** confirmed that the important role of EGb's antioxidant and anti-inflammatory properties against cisplatin -induced nephrotoxicity. Similarly, **Abd-Eldayem *et al*., (2016)** demonstrated that EGb761 has antioxidant and anti-inflammatory actions. It has nephroprotective action through the reduction of inflammatory markers and oxidative stress. These results strongly supported that GB has powerful antioxidant, anti-inflammatory and protective agent against Cis induced toxicity. There are many reports in the literature about the antioxidant and the anti-inflammatory properties of GB **(Okuyan *et al*., 2012)** and **(Noor-E-Tabassum *et al*., 2022)**.In conclusion, the results of the present study indicated that ginkgo biloba leaves have an activity against inflammation in the levels 2 and 4% levels group of normal rats. Moreover, GBL caused a significant decrease pedal inflammation at 4% level group of nephrotoxicity rats.

Results recorded in **Table 7** showed that the effect of ginkgo biloba leaves powder on serum mineral contents of normal and nephrotoxicity rats. Administration of cisplatin to rats significantly ($p< 0.05$) reduced serum mineral contents (calcium, potassium, iron, sodium, copper, and zinc) compared to negative control group. This was in congruence with the findings reported by **Maheshwari *et al*., (2013)** who stated that Cisplatin nephrotoxicity was associated with hypocalcaemia in the rat. **Abdel-Gayoum and Ahmida, (2018)** suggested that Cisplatin reduced the renal function, which was reflected with significant decrease serum calcium. These results were in the same line with the results of **Marklund *et al*., (2004)** data indicated reduced serum potassium in the cisplatin-treated animals. **(Lajer *et al*., 2005)** mentioned that cisplatin treatment also exerted a negative effect on total potassium (K) balance. Also, the obtained findings agreed with **(Abdel-Gayoum and Ahmida, 2017)** who revealed that significant reductions were observed in the serum levels of potassium and calcium due to Cisplatin treatment. Cisplatin-based therapy results in a cumulative anemia that is disproportionate to the effects on other blood cells **(Wood and Hrushesky, 1995)**. Cisplatin causes intracellular iron deficiency through direct inhibition of the master regulator of iron metabolism, iron regulatory protein 2 (IRP2) with marginal effects on iron regulatory protein 1 (IRP1). Collectively, cisplatin is an inhibitor of IRP2 that induces intracellular iron deficiency **(Miyazawa *et al*., 2019)**. In a study by **(Yousif *et al*., 2021)** observed that Cisplatin drug can affect on the hematological parameters and induced anemia, neutropenia and thrombocytopenia. Mean serum sodium and potassium levels were decreased after the chemotherapy. P value (<0.0001) was found to be highly significant as found in the present results were confirmed by **(Das *et al*., 2016)**. In the same line a study by **Pham *et a*l., (2017)** provided evidence that serum sodium was decreased after Cisplatin therapy. In a study by **DeWoskin and Riviere, (1992)** indicated that cisplatin therapy may cause an increased renal excretion of copper and may result in copper depletion. **Akutsu *et a*l, (2012)** demonstrated the serum concentration of copper was significantly decreased by Cisplatin therapy. Cisplatin has been reported to increase urinary zinc excretion and reduce serum zinc levels enzymes as found in the present study that supported by **(Sweeney *et al*, 1989)** and **(Manns-Shildt, 1996)**.Results in table **(7)** indicated that normal rats received ginkgo biloba leaves powder by 1% level showed no adverse changes in serum mineral contents (calcium, potassium, iron, sodium, copper, and zinc) as compared to negative control. But there was a significant rise in serum mineral contents (calcium, potassium, copper, and zinc) of normal rats demonstrated that ginkgo biloba leaves powder in the two levels 2 and 4%, may be attributed to the effects of ginkgo biloba leaves supplemented. There are some studies in the literature showing that dietary supplementation of GL and EGB increased the utilization of nutrient and energy in broilers in a dose-dependent manner (**Zhang *et al*., 2012** and **Ren *et al*., 2018)**.

The results of mineral analysis on whole Ginkgo biloba dried leaves showed presence of high concentrations of the macro minerals especially calcium and magnesium and followed by phosphorous, potassium, sodium, iron, zinc, manganese, copper and selenium as found in the present study that supported by **Nwosu *et al*., (2018)** and **Lysiuk et *al*., (2018)** who mentioned that GBL might be recommended for a wider application also as a food supplement. From the results presented in table **7**, it is evident that there was no significant rise between nephrotoxicity rats received ginkgo biloba leaves powder and nephrotoxicity control group in the three levels 1 and 2%, whereas level 4% showed significantly increased ($P<0.05$) compared with nephrotoxicity control group. In a study by **Jiménez-Triana *et al*., (2015)** who confirmed that cisplatin clearance by the kidney depends upon glomerular filtration and tubular secretion. Cisplatin accumulates in the kidney at higher concentrations than in the blood and other organs, contributing to kidney injury. **Jo et al., (2021)** data indicated that the kidneys play a crucial role in maintaining our health. They regulate the homeostasis of minerals such as calcium (Ca), magnesium (Mg), phosphorus (P), and sodium (Na) through filtration and reabsorption processes. Previous studies have documented that ginkgo biloba extract was found to be effective in Cisplatin-induced nephrotoxicity **(Gulec *et al*., 2006)** and **(Okuyan *et al*., 2012)**. A similar study was done by **(Wei *et al*., 2022)** observed that EGb could protect against acute renal injury induced by cisplatin. May be leading to the beneficial effects of ginkgo leaves, it was contained important macro- and micronutrients such as Ca, Mg, K, Al, Fe, Cu, Mn, Zn, Mo, Co, I, Se, which are necessary for the vital activity of the human body and normal metabolism **(Gafurdjanov *et al*., 2021)**. Our results have evidenced that ginkgo biloba leaves have beneficial effects on serum mineral contents of normal and nephrotoxicity rats, may be leading to it was contained high concentrations of minerals.

Table (1) Chemical composition of Ginkgo biloba leaves powder.

Compounds	mg/100g
Calcium (Ca)	1990.25
Potassium (K)	1157.00
Iron (Fe)	37.36
Sodium (Na)	375.82
Copper (Cu)	0.552
Zinc (Zn)	0.768

Table (2) Effect of Ginkgo biloba leaves powder on initial body weight (IBW), final body weight, feed intake (FI), body weight gain (BWG) and feed efficiency ratio (FER) of normal and nephrotoxic rats.

Parameters Groups	IBW	Final BW	FI (g/d/rat)	BWG (%)	FER
Negative Control	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
Positive Control	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

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.

Table (3) Effect of Ginkgo biloba leaves powder on serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) of normal and nephrotoxic rats.

Parameters Groups	AST	ALT
	(U /L)	
Negative Control	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}
Positive Control	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}

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.

Table (4) Effect of Ginkgo biloba leaves powder on creatinine, urea, total protein and albumin of normal and nephrotoxic rats.

Parameters Groups	Creatinine mg/dL	Ure mg/dL	Total Protein mg/dL	Albumin mg/dL
Negative Control	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
Positive Control	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

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.

Table (5) Effect of Ginkgo biloba leaves powder on malondialdehyde (MDA) and glutathione (GSH) of normal and nephrotoxic rats.

Parameters Groups	MDA (U/mL)	GSH (m mol/mL)
Negative Control	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
Positive Control	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

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.

Table (6) Effect of ginkgo biloba leaves powder on formalin-induced inflammation for different times on the paw's thickness of normal and nephrotoxic rats.

Periods Groups	2 Hours	4 Hours	6 Hours
Negative Control	3.18±0.63c	3.12±0.12c	3.01±0.17c
1% GB	3.21±0.57c	3.10±0.18c	2.96±0.15c
2% GB	3.15±0.15c	2.36±0.15d	2.16±0.17d
4% GB	3.35±0.62c	2.07±0.07d	1.95±0.27d
Positive Control	5.42±0.13a	5.84±0.14a	7.16±0.24a
1% GB	5.31±0.18a	4.01±0.21a	3.61±0.11b
2% GB	5.20±0.19ab	3.77±0.07ab	3.55±0.15b
4% GB	4.96±0.21b	3.26±0.09bc	3.17±0.17bc

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.

Table (7) Effect of Ginkgo biloba leaves powder on serum mineral contents of normal and nephrotoxic rats.

Minerals Groups	Calcium (mg/ml)	Potassium (mmol/L)	Iron (mg/dl)	Sodium (mmol/L)	Copper(mg/ml)	Zinc (Mg/dl)
Negative Control	8.38±0.12c	3.87±0.16bc	168.85±1.52a	140.68±1.72a	0.62±0.02b	0.65±0.01bc
1% GB	8.64±0.18c	3.67±0.22cd	169.85±0.87a	141.10±1.29a	0.62±0.04b	0.66±0.02bc
2% GB	9.19±0.29ab	4.74±0.20a	170.85±1.93a	143.47±1.39a	0.73±0.03ab	0.82±0.03a
4% GB	9.55±0.27a	5.03±0.11a	172.83±1.69a	144.53±1.03a	0.81±0.02a	0.92±0.01a
Positive Control	6.77±0.16d	3.12±0.18d	75.13±1.25d	125.93±1.08b	0.35±0.02c	0.35±0.02d
1% GB	6.89±0.11d	3.22±0.08cd	79.53±2.04d	126.32±1.06b	0.39±0.02c	0.37±0.02d
2% GB	7.17±0.22d	3.20±0.11cd	89.86±1.11c	127.76±1.75b	0.41±0.04c	0.58±0.02c
4% GB	8.14±0.17bc	4.50±0.11ab	135.18±1.77b	141.41±1.13a	0.61±0.02b	0.71±0.02b

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.

Conclusion

The current study suggests that Ginkgo biloba leaves contain many active constituents and produce hepatoprotective, renoprotective, antioxidant and anti-inflammatory effects in nephrotoxic rats. These leaves also improve body weight gain and feed efficiency ratio. Therefore, intake of Ginkgo biloba leaves as a powder may be beneficial for patients who suffer from nephrotoxicity.

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