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Role of CoQ_{10} on Some Biochemical and Histological Aspects of Kidney in Rats Exposed to Sodium Fluoride

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Abstract

This experiment was aimed to investigate the role of CoQ10 to alleviating the functional alterations of kidney - induced by sodium fluoride (NaF) in male rats. Twenty adult male Wister albino rats were randomly assigned into four equal groups and treated for 42 days daily as follows: first group was received drinking tap water and intubated with DMSO 1% and serving as control (group C); second group (group G1) received sodium fluoride 100ppm in drinking tap water ; third group (group G2) received sodium fluoride 100ppm in drinking tap water plus intubated 10 mg /Kg. B.W of CoQ10 orally , whereas fourth group (group G3) intubated 10 mg /Kg. B.W of CoQ10 only. Fasting blood samples were collected at 0, 21, and 42 days of experimental periods. Then sera was isolated for estimated serum creatinine, blood urea nitrogen (BUN) and peroxynitrite radicals concentrations, as well as catalase activities has been measured. At the end of the experiment the animals were sacrificed and sections from the kidney were taken for histopathological examination. The results revealed that rats received NaF (group G1) for 42 days caused significant decrease in body weight and serum catalase activity , while a significant increase in the concentrations of serum creatinine, blood urea nitrogen (BUN) and peroxynitrite radicals accompanied with histopathological alterations of kidney were showed as compared to other experimental groups . On the other hand, administration of CoQ10 to groups G2 showed an improvement of physiological and histological alterations and keeping the kidney functions around the normal levels, manifested its protective effects against deleterious effects of NaF. It could be concluded that these results confirmed the antioxidant properties of CoQ10 against nephrotoxicity induced by NaF in adult rats.

Key Words: kidney function, sodium fluoride, CoQ10, antioxidant enzymes.

دور CoQ10 وعلى بعض الجوانب الكيميائية والنسيجية لالكلى في الفئران المعرضة للفلوريد الصوديوم

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الخلاصة:

هدفت هذه التجربة إلى التحقق من دور CoQ10 في التخفيف من التغيرات الوظيفيه للكلى الناتجة عن فلوريد الصوديوم (NaF) في ذكور الجرذان. تم توزيع 20 جرذاً ذكراً بالبغاً بشكل عشوائي على أربع مجموعات متساوية وعوملت لمدة 42 يومًا يوميًا على النحو التالي: المجموعة الأولى اعطيت مياه الشرب ,وجرعت بتركيز 1% من مادة DMSO وأعتبرت كمجموعة تحكم (المجموعة C). أما المجموعة الثانية (G1) فقد

اعطيت 100 جزء بالمليون من فلوريد الصوديوم في مياه الشرب ؛ في حين تلقت المجموعة الثالثة (G2) فقد اعطيت 100 جزء بالمليون من فلوريد الصوديوم في مياه الشرب بالإضافة إلى تجريعها فمويا 10 ملغ / كغم. من وزن الجسم من CoQ10 ، بنما المجموعة الرابعة (G3) جرعت فمويا 10 ملغ / كغم. من وزن الجسم من CoQ10 . تم جمع عينات الدم في 0 و 21 و 42 يوما من الفترات التجريبية. ثم عزل المصل لغرض قياس تركيز الكرياتين ، يوريا الدم (BUN) وتركيز جذر البيروكسينيتريت ، أضافة الى تقدير نشاط انزيم الكاتلاز. في نهاية التجربة تم التضحية بالحيوانات وأخذت أجزاء من الكلى لفحص الأنسجة. أوضحت النتائج أن الجرذان التي اعطيت NaF (المجموعة G1) لمدة 42 يومًا تسببت في انخفاض ملحوظ في نشاط الكاتلاز في الدم ، في حين تسبب فلوريد الصوديوم بزيادة معنوية في تركيز كرياتينين المصل ونتروجين اليوريا في الدم وجذر البيروكسينيتريت مصحوبة بتحسن نسجي للكليتين مقارنة مع المجموعات التجريبية الأخرى. من ناحية أخرى ، أظهر CoQ10 تحسنا في التغيرات الفسيولوجية والنسيجية والحفاظ على وظائف الكلى حول المستويات الطبيعية ضد الآثار الضارة لفلوريد الصوديوم . ويمكن الاستنتاج أن هذه النتائج أكدت على الخصائص المضادة للأكسدة ل CoQ10 ضد السمية الكلوية الناجمة عن NaF في الجرذان البالغة.

الكلمات المفتاحيه : وظائف الكلى ، فلوريد الصوديوم ، CoQ10 ، مانعات الاكسدة.

Introduction

Coenzyme Q10 is a unique lipid soluble vitamin-like substance synthesized endogenously (1) found with highest concentrations in heart, liver, kidney, pancreas and brain, with the lowest concentration in the lungs (2 and 3). It has been found that CoQ10 play unique role in mitochondrial bioenergetics (4) and in the electron transport chain (ETC) as an electron carrier from enzyme complex I and enzyme complex II to complex III (5).Thereby, it is participates in aerobic cellular respiration and generated energy in the form of ATP for cellular functions and metabolism (1 and 5), since no other molecule can perform this function. Wherefore, CoQ10 considered as the third most sold dietary supplement in the United States after omega-3 fatty acids and multivitamins (6). Mutations in the genes involved in the biosynthesis of CoQ10 causing disruption of mitochondrial bioenergetics and induced oxidative stress (4 and 7) which related to various types of mitochondrial diseases.

Many researchers suggested that dietary supplement of CoQ10 counteracting some of tissue damage induced by free radicals such as nephrotoxicity , inflammation and apoptosis (8and9), liver and heart injury (10and11) via its cytoprotective , antioxidant and anti-inflammatory properties (12,13and 14). Also, exogenous supplementation of CoQ10 ameliorating the bioenergetics impairment in some mitochondrial myopathies and in cardiomyopathy, may be due to an increase respiratory rate (15 and 16).

On the other hand, administration of CoQ10 (Ubiquinol) caused an improvement of renal injury and a decrease in renin-aldosterone axis in patients with lithiasis(17) and effectively ameliorates renal function probably due to its antioxidant effect (8). Thus, ubiquinol may be a candidate for the treatment of patients with kidney disease (18).

Fluoride anions are present in ground water and drinking water and can be transported by wind due to dust, fertilizers and volcanic activity (19). Fluorine is used in aluminum production (20), in pesticides, fungicides, insecticides adhesives and glues (21). Furthermore, its compounds are mostly used to keep from oral caries (21) and to reduces the decay of teeth enamel (23). Fluoride administration substantially enhanced fluoride accumulation, caused metabolic disturbance activities and lipid peroxidation(LPO) via inhibit

certain antioxidant enzymes and reduce total serum protein (24,25 and 26). The toxic level of fluoride have been associated with nephrotoxicity in animals and humans (27 and 28) that may be due to release of fluoride from fluorine-containing substances. At the higher concentration of fluoride , the kidney function was impaired and exhibited to depressed clearance of crystalloids, enhanced elimination of amino acids and cause inhibition of enzymes that required for action of antidiuretic hormone (29). Considering all of these facts, the aim of the present work was designed to investigate the effect of CoQ10 in ameliorating the kidney dysfunctions in sodium fluoride treated rats.

Materials and Methods

In this experiment twenty adult male Wister albino rats, weighed (190g. - 250g.) were used . Animals in all periods of the experiment were housed in plastic cages in the animal house of the College of Veterinary Medicine - University of Baghdad and had free access to pellets diet and water *ad libitum* water along the experimental period. Rats were divided randomly into four equal groups and were handled daily as follows for 6 weeks : group- C: rats in this group rats were received ordinary tap water plus intubated dimethylsulfoxid (DMSO) 1% and served as control ; group-G1: in this group rats were administered 100ppm of sodium fluoride in tap water ; while rats in group-G2 were intubated daily 10 mg/kg BW of CoQ10 plus received ordinary tap water containing 100 ppm of NaF and group-G3 were intubated CoQ10 only at the same dose of group-G2.

Fasting blood (for 10-12 hr.) samples were collected at zero, 21 and 42 days of the experimental periods. Blood was drawn by retro-orbital Sinus technique according **(30)** from anesthetized rats by intramuscular injection of (Ketamine 90 mg/kg B.W. and Xylazine 40mg/kg B.W.) using Micro-Hematocrit capillary tubes. Blood samples were kept in gel tube, then centrifugation for 15 minutes at 3000 rpm. Serum samples were isolated and frozen at -18°C until analysis. By using kits (products of Bio System , Agappy-Switezrland) for estimated the concentrations of serum creatinine according to (31), blood urea nitrogen(BUN) as described by (32). Furthermore, serum peroxynitrate radical concentration was measured according to (33) and serum catalase activity was determined according to the method of (34). At the end of experiment rats were anesthetized and sacrificed and immediately kidney were excised, blotted, and preserved in 10% formalin solution, then embedded in paraffin, slices and staining with hematoxylin-eosin method for histological examination (35).Statistical analysis of data was done using SPSS software version 9.1. using Two-Way Analysis of Variance (ANOVA) followed by post hoc least significant difference (LSD) test. Results were expressed as mean ± SE. For all analysis, the level of statistical a significance was set at $P<0.05$ (36).

Results:

The results of the present work showed a significant ($p<0.05$) elevation in serum creatinine concentration at 21 and 42 days of the treatment in G1 and G2 groups compared to control and G3 groups (figure 1-A). At the end of the experiment a correction of kidney dysfunction (i.e. decrease in serum creatinine) was observed in group G2 that received NaF plus CoQ10 (0.61±0.01) comparing to the mean value in G1 group (0.85 ±0.01).

In the present study, a significant ($P< 0.05$) elevation in serum BUN concentration at 21 and 42 days of the

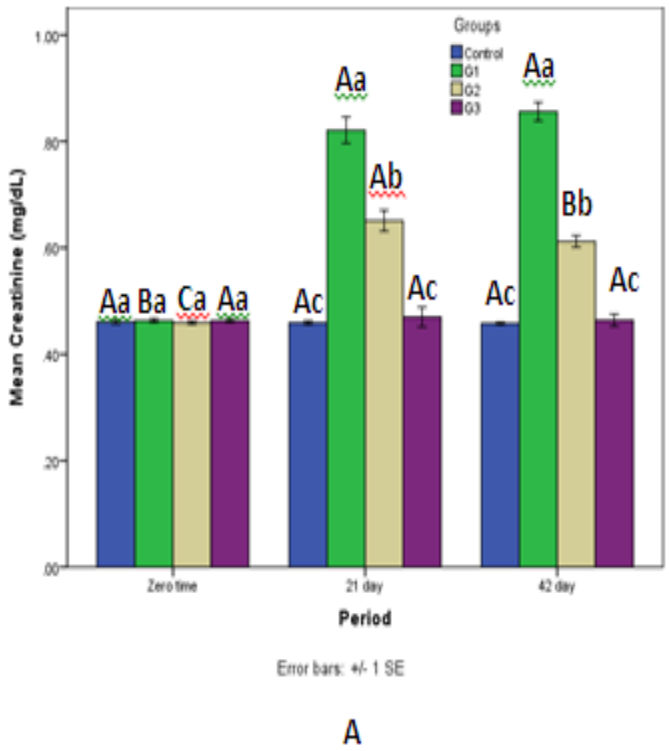
experiment in group G1 and group G2 was observed in comparison with control and G3 groups (figure 1-B). Further, no significant ($P > 0.05$) differences was recorded between control and G3 groups at two treated periods (21 and 42 days) of the experiment. In comparison between periods, G1 and G3 treated groups recorded significant ($P < 0.05$) increase in serum BUN at 21 and 42 days compared to zero point.

Rats received NaF in drinking water group G1 and that received NaF plus intubation of 10 mg/ kg B.W. of CoQ_{10} (group G2) showed significant ($P<0.05$) increase in serum

On the other hand , the results showed significant ($P<0.05$) decrease in serum CAT activity after 21 days in G1 and G1 treated groups and).

peroxynitrite concentration started at 21 days of treatment in comparison with control and G3 groups (figure 1-C) and continued in its elevation until the end of the experiment at 42 days. Otherwise , a significant ($P<0.05$) decrease in this parameter was observed at 42 days in group G3 with the mean value (32.39±1.0) comparing to control (36.09±1.29). In comparison between periods, control and G2 groups showed no significant ($P>0.05$) differences between the experimental periods ,whereas sodium fluoride treated group (G1) recorded significant ($P<0.05$) increase at day 42 comparing to zero and 21 days.

continued in its decrement until the end of experiment in the same groups (figure 1-D



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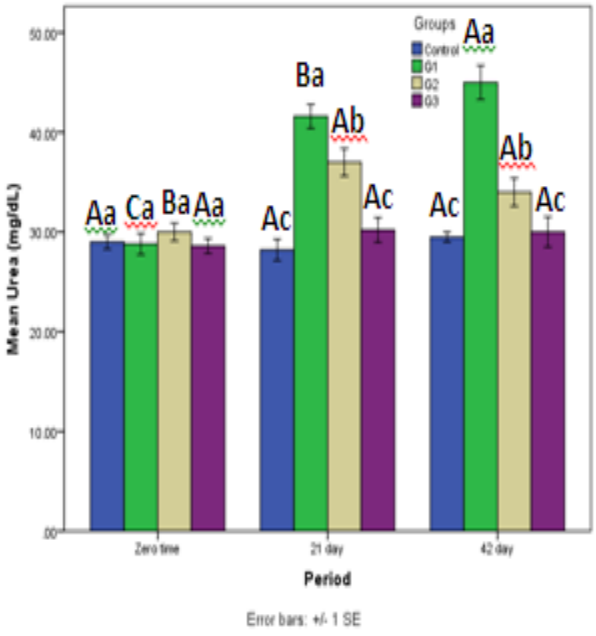

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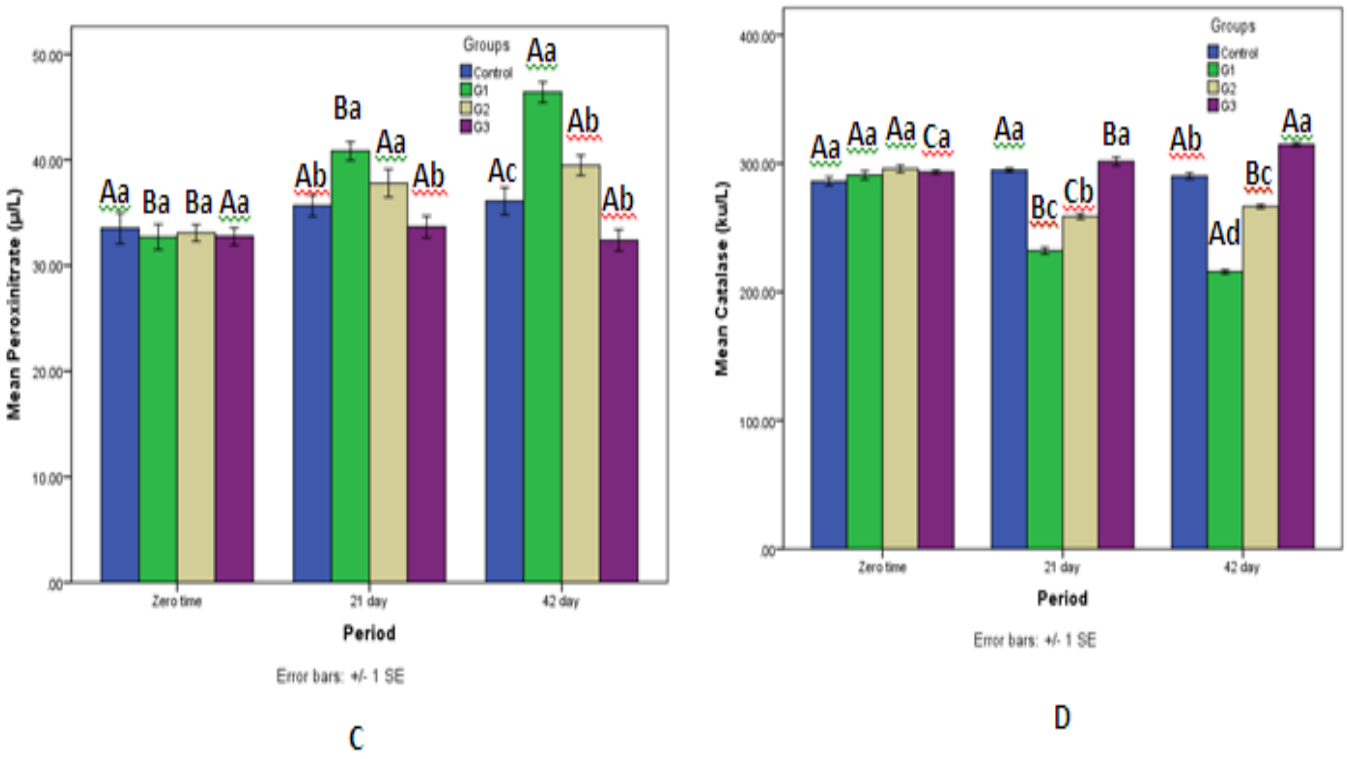

Figure (1) Effect of sodium fluoride and CoQ10 on serum concentrations of (A) creatinine, (B) blood urea nitrogen(BUN), (C) peroxynitrite and (D) catalase in adult male rats.

Values are represented as mean ±SE. Different small letters denotes the presence of significant differences ($p > 0.05$) between groups. Different capital letters denotes the presence of significant differences($p > 0.05$) within group. Control: rats received tap water; G1: rats received tap water contain NaF 100 ppm; G2: rats received tap water contain NaF100 ppm Plus orally garaged CoQ10 (10 mg/kg B.W.); and G3: rats orally garaged CoQ10 (10 mg /kg B.W.).

Histopathological examination of kidney sections of control rats showed normal structure of the kidney with devoid of pathological lesions figure (2). In sodium fluoride treated rats (group G1) kidney sections showed renal damage characterized by hydropic generation with interstitial inflammatory infiltration of mononuclear cells (MNCs) figure (3) and dilation of Bowman's space may be due oxidative stress with presence of hyaline casts in renal tubules compared to figure-2. Whereas, rats exposed to sodium fluoride plus CoQ10 (group G2) caused an ameliorating the kidney damage characterized by decrease of hydropic generation and inflammatory cell infiltration with mild congestion and slight edema figure (4). No pathological changes with normal architecture of kidney tissue sections has been showed in rats kidney intubated CoQ10 only (figure 5) as compared to control

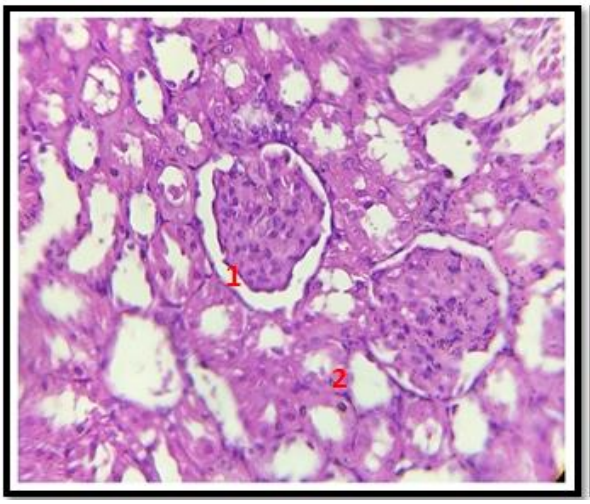

Figure 2: Cross section of rat kidney of control showed normal cellular and tubular structure kidney. 40X (H & E stain).

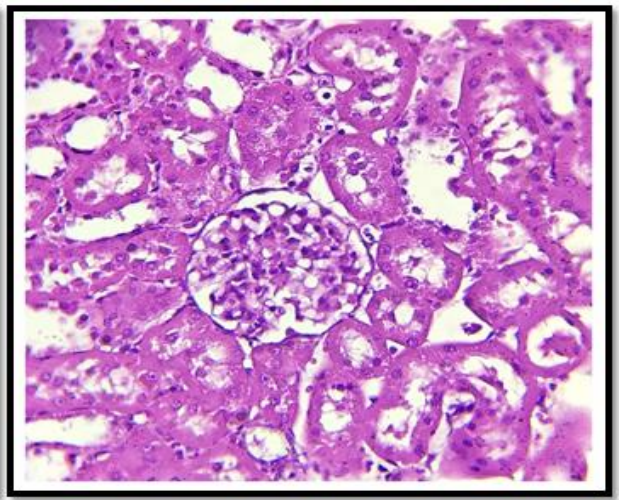

Figure 3 : Cross section of rat kidney treated with NaF (group G1) for 42 days, revealed renal damage characterized with interstitial inflammatory infiltration of mononuclear cells (MNCs) (1) and dilation of Bowman's space (2)and distal tube (3) 40X (H & E stain) .

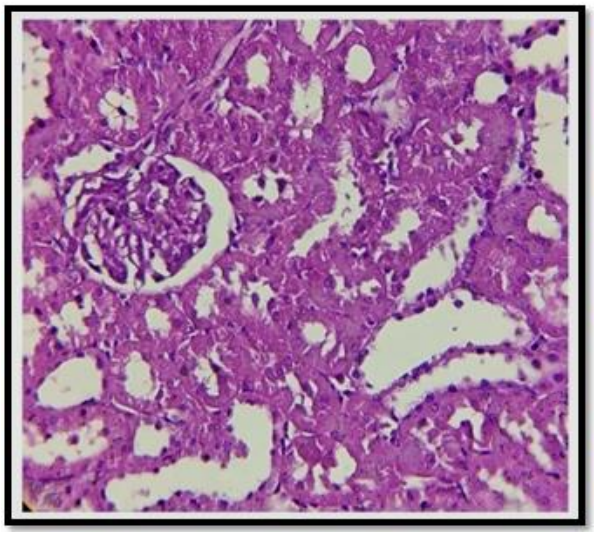

Figure 4: Cross section of rat kidney treated with NaF and CoQ10 (group G2) for 42 day represents mild dilation of Bowman space (1) with slight edema (2) 40X (H & E stain).

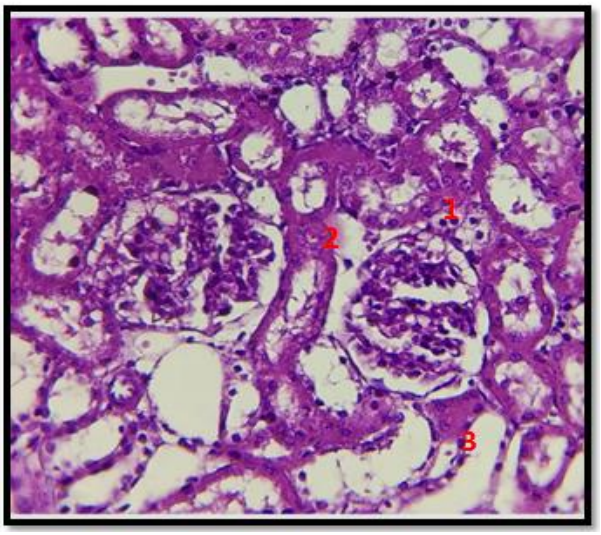

Figure 5: Cross section of rat kidney treated with CoQ10 (group G3) for 42 day. Shows normal histological structure of the kidney without of pathological lesions 40X (H & E stain).

Discussion

The kidney is a target organ for potential fluoride toxicity. Data in the present study showed that NaF caused significant increase in serum creatinine and BUN (group G1). These results was agreement with (37). It has been shown that fluoride ions caused directly inhibit glycolysis, by inhibiting the enzyme enolase in renal cells, which is often compensated by using alternative energy-producing pathways that leading to renal cellular dysfunctions (38) correlated with increased calcium and phosphate urinary excretion (39), as well as, an increased degradation of collagen and/or inhibition of collagen synthesis by NaF (40) leading to alterations in glomerular filtration rate (GRF) (41). The results manifested a significant reduction in serum creatinine and BUN concentrations in group G2 compared to group G1, indicating that CoQ10 could be reversed the toxic effect of NaF on renal tubular cells and improvement kidney functions due its antioxidants properties

Concerning the oxidant/antioxidant status, the result showed a significant decrease in serum catalase activities with significant increase in peroxynitrite concentration in group G_1 compared to control suggesting a case of oxidative stress induced after exposure to NaF. This result is in accordance with other studies (25,42 and 43). Further, it has been reported that fluoride intoxication resulted to induce oxidative stress (OS) with an excessive generation of reactive oxygen species (ROS) such as superoxide anion (O_2^-), hydrogen peroxide (H_2O_2) and hydroxyl radicals ($OH^·$) (44), which have been implicated in the initiation and/or progression of nephrotoxicity (45). Such changes in these biomarkers related with oxidant–antioxidant status and histological structures of kidneys in group G1 that may be caused LPO, DNA and proteins damage leading to renal dysfunction (41 and 46). So, it impair the catalase activity in catalyzes of hydrogen peroxide to water and oxygen and prevent the protecting of cell membrane against LPO induced by ROS (42). Peroxynitrite is a key element in refraining the contrasting parts of NO in pathology and physiology. It is an oxidant and nitrating agent, so when generate in excess in a long period will result in damage a wide range of cell constituent (47). Oxidation of cofactors of antioxidant enzyme either by direct or free-radical-dependent mechanisms causing depletion of these enzymes (48) leading to disruption of cell signaling pathways and induction of both cell necrosis and apoptosis (47). Otherwise, elevation in environmental oxidants including NaF caused elevation in of ROS give rise to mitochondrial dysfunction such as, loss of mitochondrial transmembrane potential, release of cytochrome C and calcium ions from mitochondria, leading to activation of caspase-3 and nuclear condensation with elevation of peroxynitrite (49and 50).

A significant increase in the activity of serum CAT enzyme (group G2) compared to G1, indicating a role of CoQ10 in attenuating oxidative stress-induced by NaF. Such results came in accordance with (17, 51 and 52)**.** CoQ10 is an important micronutrient acting on the electron transport chain of the mitochondria through supporting the synthesis of adenosine triphosphate (ATP) and acting as a potent antioxidant (53 and 54). The protective role of CoQ_{10} was indicting by preventing a significant loss of mitochondrial mass via ; increasing mitochondrial number and volume density, suggesting an induction of mitochondrial biogenesis (55) , or by maintaining the mitochondrial membrane potential, supporting synthesis of ATP and inhibiting ROS generation, thereby, may

be protecting the cells against oxidative stress (53,56 and 57). So, it could be suggested that oxidative stress in group (G1) can be ameliorating/suppressed with CoQ10 treatment attributed to its antioxidant properties.

References

1. Littarru, G.P and Tiano, L . (2007). Bioenergetic and antioxidant properties of coenzyme Q10 : recent developments. Mol biotechnol., 37(1):31-7.
2. Linnane, A.W.; Kopsidas, G.; Zhang, C.;Yarovaya, N.; Kovalenko, S.; Papakostopoulos, P.; Eastwood, H.; Graves, S. and Richardson, M. (2002). Cellular redoxactivity of coenzyme Q10: effect of CoQ10supplementation on human skeletal muscle. Free Radic Res., 36(4): 445–453.
3. Butler, M.G.; Dasouki, M.; Bittel, D.; Hunter,S.; Naini, A. and DiMauro, S. (2003). Coenzyme Q10 levels in Prader-Willi syndrome:comparison with obese and non-obese subjects. Am J Med Genet., 119(2); 168–171.
4. Ben-meir, A.; Burstein, E.; Borrego-Alvarez, A.; Chong, J.; Wong, E.; Yavorska, T.; Naranian, T.; Chi,M.;Wang, Y.; Bentov, Y. (2015). Coenzyme Q10 restores oocyte mitochondrial function and fertility during reproductive aging cell, 14 887-895.
5. Promise, S.; Banua1,A., Asadulla, S. and Subbaiah, M.V. (2016). Coenzyme Q10 – A Review of Its. IOSR Journal of pharmacy and Biological Sciences., 11(3) Var. I : 14-19 .
6. Acton, A. (2013). Enzymes and Coenzymes-advances in research and application. Scholarly edition.
7. Kawamukai, M. (2015). Biosynthesis of coenzyme Q in eukaryotes. Biosci. Biotechnol. Biochem, 80, 23-33.
8. Fatima, S.; Al-Mohaimeed, N.; Al-Shaikh Y.; Tyagi P.; Banu N.; Hasan S. and Arjumand ,S. (2016). Combined treatment of epigallocatechingallate and coenzyme Q10 attenuates cisplatin-induced nephrotoxicity via suppression of oxidative/nitrosative stress, inflammation and cellular damage. Food Chem Toxicol.94:213-220.
9. Fouad, A.A. and Jresat, I. (2012). Hepatoprotective effect of coenzyme Q10 in rats with acetaminophen toxicity. Environ Toxicol Pharmacol;33(2):158-67.
10. Ashkani-Esfahani,S.; Bagheri, F.; Emami, Y.; Esmaeilzadeh, E.; Azarpira, N.; Hassanabadi, N.; Keshtkar, M.; Farjam, M.; Koohi-Hosseinabadi, O. and ONoorafshan, A. (2016). Protective effects of co-enzyme Q10 on thioacetamide-induced acute liver damage and its correlation with behavioral, biochemical , and fathological factors. Iran Red Crescent Med J., 19;18(8):e29166.
11. Ulla, A.;Mohamed, M.K; Sikder, b.; Rahman ,A.F.M.T.; Sumi, F.A.; Hossain, M.; Reza, H.M.;Rahman,G.M.S. and A lam,M.D.A. (2017). Coenzyme Q10 prevents oxidative stress and fibrosis in isoprenaline induced cardiac remodeling in aged rats. BMC PharmacolToxicol., 18: 29.
12. Ekin, S. and Bayramogluo, M. (2013). Cytoprotective effects of boric acid and coenzyme Q10 therapy on induced pulmonary fibrosis in response to intratracheal administration of bleomycin in rats. Fresen Environ Bull ., 22(8): 2428-2434.
13. Mirmale, k,S.A.; Gholamrezaei, B.A.; Yavari, H.; Kardeh, B.; Parsa, Y.; Salimi-Tabatabaee, S.A.;Yadollah-Damavandi, S.; Paras,T.; Shahverdi, E. and Jangholi, E. (2016). Antioxidant and Anti-Inflammatory Effects of

Coenzyme Q10 on L-Arginine-Induced Acute Pancreatitis in Rat.Oxid Med Cll Longey., 5818479. doi: 10.1155/2016/5818479.

14. Thanh, H.N.; Minh,H.P.T.; Duc,L.V. and Thanh,T.B. (2016). Protective effect of coenzyme Q10 on methamphetamine-induced neurotoxicity in the mouse brain. Trends in Medical Research, 11: 1-10.
15. López-Lluch, G.; Rodríguez-Aguilera, J.C.; Santos-Ocaὴa, C.; Navas, P. (2016), Is conenzyme Q a key factor in aging?Mech. Ageing Dev. ,131,225-235.
16. Mortensen SA, Rosenfeldt F, Kumar A, Dolliner P, Filipiak KJ, Pella D, Alehagen U, Steurer G, GP L, Q-SYMBIO Study Investigators. (2014). The effect of coenzyme Q10 on morbidity and mortality in chronic heart failure: results from Q-SYMBIO: a andomized double-blind trial. JACC Heart Fail. ;2(6):641–9. doi: 10.1016/j.jchf.06.008.
17. Carrasco, J.; Anglada, F.J.; Campos, J.P.; Muntané, J.; Requena, M.JJ. and Padillo, J. (2014). The protective role of coenzyme Q10 in renal injury associated with extracorporeal shockwave lithotripsy: a randomised, placebo-controlled clinical trial. BJU Int., 113: 942–950.
18. Ishikawa, A.; Kawarazaki, H.; Ando, k.; Fujita, T. and Homma, Y. (2011). Renal preservation effect of ubiquinol, the reduced form of coenzyme Q10. Clin Exp Nephrol., 15:30-3.
19. ATSDR (Agency for Toxic Substances and Disease Registry). (2014). Medical management guidelines for hydrogen fluoride (HF). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.
20. Mueller, W.H. (2001). Fluoride compounds, inorganic, sodium. Encyclopedia of chemical Technology. John Wiley and sons, inc.
21. Budavari, S. (1989). The Merck index: an encyclopedia of chemicals, drugs, and biologicals. 11thed.. Merck Co., Rahway, N.J. p: 8565.
22. Dabrowska, E.; Letko, R.and Baluonowska,M. (2006). Effect of sodium fluoride on the morphological picture of the rat liver exposed to NaF in drinking water. Advances in Medical Sciences. 51(1): 91- 95.
23. Ten Cate, F.M. (2013). Contemporary perspective on the use of fluoride products in caries prevention. British Dental Journal 214, 161 – 167.
24. Abdel-Wahab, W.M. (2013). Protective effect of thymoquinone on sodium fluoride- induced hepatotoxicity and oxidative stress in rats. The Journal of Basic and Applied Zoology, 66: 263–270.
25. Ali, E.H. and Al-Okaily, B. N. (2016). The protective role of pomegranate seeds oil (Pometone) on serum protein in sodium fluoride treated rats. IJVM.,40(1):61-68.
26. Mohammed, I.A. and Al-Okaily, B.N. (2017) . Effect of sodium fluoride on liver functions of rats and amelioration by CoQ10. Journal of Entomology and Zoology Studies . 5(5): 887-893.
27. Bouaziz, H.; Ghorbel, H.; Kretata, S.; Guermazi, F. and Zeghal, N. (2005). Toxic effects of fluoride by maternal ingestion on kidney function of adult mice and their suckling pups. Fluoride, 38: 23–31.
28. Anjum, K. M.; Mughal, M.S.; Sayyed, U.; Yaqub, A.; Khalique, A.; Rashid, M.A.; Yousaf, M. Z. and Mumtaz, M. Z. (2014). Influence of increasing fluoride

dose rates on selected liver and kidney enzymes profile in domestic chicken (Gallus domesticus). J Animal Plant Sci., 24(1): 77-80.
29. Briker,E.; Grucka-Mamczar, E.; Zwirska-Korczala, K.; Fiolka, J.; Stawiarska-Pieta, B.; Kasperczyk, D. and Kasperczyk, A. (2006). Influence of sodium fluoride and caffeine on the kidney function and free-radical processes in that organ in adult rats.Bio Trace Elem Res., 109(10:35-48.
30. Para suraman, S.; Raveendran, R. and Kesavan, R. (2010). Blood sample collection in small laboratory animals. J Pharmacol Pharmacother., 1 (12): 87-93.
31. Burtis, C.A.; Ashwood, E.R. and Bruns, D.E. (1999).Tietz textbook of clinical chemistry and molecular diagnostics, 3rd ed, AACC.Philadelphia,1915-1916.
32. Chaney, A.L. and Marbach, E.P. (1962). Modified reagents for determination of urea and ammonia. Clin Chem., 8: 130-132.
33. Vanuffelen, B. E.; Van Der Zee, J.; De Koster, B .M.; Vansteveninck, J. and Elferink, J .G. (1998). Intracellular but not extracellular conversion of nitroxyl anion into nitric oxide leads to stimulation of human neutrophil migration. Biochem. J., 330(2):719-722.
34. Goth, L. (1991). A simple method for determination of serum catalase activity and revision of reference range. Clin Chim Acta., 196:143-152.
35. Lee, J.C.; Son, Y.O.; Choi, K.C.; Jang, Y.S. (2006). Hydrogen peroxide induce Apoptosis of BJAB cell due to formation of hydroxyle radicals via intracellular Iron mediated fenton chemistry inglucose oxidase mediated oxidative stress. Mol.Cell., 22 (1) :21- 29.
36. Snedecor, G.W. and Cochran, W.G. (1973). Statistical Methods. 6th ed. the Iowa state University press.
37. Iheka, C. U.; Onyegeme-Okerenta, B. M. and Anacletus F. C. (2016). Impact of fluoride toxicity and ameliorative effects of some antioxidants on selected biochemical indices of male rats. AASCIT Journal of Health; 2(6): 87-92.
38. Goligorsky, M.S.; Brodsky, S.V. and Noiri, E. (2002). Nitric oxide in acute renal failure: NOS versus NOS. Kidney Int., 61:855–861.
39. Santoyo-Sanchez, M.P.; Silva-Lucero, M.D.; Arreola-Mendoza, L. and Barbier, O.C. (2013). Effects of Acute Sodium Fluoride Exposure on Kidney Function, Water Homeostasis, and Renal Handling of Calcium and Inorganic Phosphate. Biol Trace Elem Res., 152:367–372.
40. Omireeni, E.A.; SiddiqiOpens, N.J.andAlhomida,A.S.(2010). Biochemical and histological studies on the effect of sodium fluoride on rat kidney collagen. Journal of Saudi Chemical Society. 14(Issue 4): 413-416.
41. Nabavi, S.M.; Nabavi, S.F.; Eslami, S. and Moghaddam, A.H. (2012). In vivo protective effects of quercetin against sodium fluoride-induced oxidative stress in the hepatic tissue. Food Chem. 132, 931–935.
42. Goschorska, A.S.; Gutowska, I.; Olszewska, M.;Baranowska-Bosiacka, I.; Rać, M.; Olszowski,T. and Chlubeka, D. (2015). Effect of sodium fluoride on the catalase activity in THP-1 macrophages. Fluoride 48(4)274-282.
43. Nabavi, S. M. (2013). In vivo protective effects of gallic acid isolated from peltiphyllumpeltatu against sodium fluoride –induced oxidative stress in rat erythrocyte.

ArhHigRadaToksikol., 64: 553-559.

44. Yamaguti PM, Simões A, Ganzerla E, Souza DN, Nogueira FN, Nicolau J. (2013). Effects of single exposure of sodium fluoride on lipid peroxidation and antioxidant enzymes in salivary glands of rats. Oxid Med Cell Longev ;2013:674593.
45. Singh, M.; Arseneault, M.; Sanderson, T.; Murthy, V. and Ramassamy, C. (2009). Challenges for research on polyphenols from foods in Alzheimer's disease: bioavailability, metabolism, and cellular and molecular mechanisms. Journal of Agricultural and Food Chemistry, 56, 4855-4873.
46. Deng, Y.B., Cui, H.M., Peng, X., Fang, J., Zuo, Z.C., Deng, J.L. and Luo, Q. (2014). Effects of high dietary fluoride on serum biochemistry and oxidative stress parameters in broiler chickens. Health, 6, 1840-1848.
47. Pacher, P.; Beckman, J.S and Liaudet, L. (2007): Nitric oxide and peroxynitrite in health and disease. Physiol. Rev.; 87(1): 315-424.
48. Ighodaro,I.O and Akinlye, O.A. (2017). First line defense antioxidant super-oxide dismutase (SOD), catalase (CAT) and gluthathionperoxidase (GPX) : Their fundamental role in the entire antioxidant defense grid. Alexandria Journal of Medicine , xxx : xxx-xxx. 9in Press).
49. Ott, M.; Gogvadze, V.; Orrenius, S. and Zhivotovsky, B. (2007). Mitochondria, oxidative stress and cell death.Apoptosis. 12(5):913-22.
50. Yang, Y .; Huang, H.; Ba, Y.; Cheng, X.M. and Cui, L.X.(2015). Effect of oxidative stress on fluoride-induced apoptosis in primary cultured Sertoli cells of rats. Int J Environ Health Res. 2015;25(1):1-9.
51. Farswan, M.; Rathod, S.P.; Upaganlawar, A.B. and Semwal, A. (2005). Protective effect of coenzyme Q10 in simvastatin and gemfibrozil induced rhabdomyolysis in rats. Indian J Exp Biol., 43(10):845-8.
52. Upaganlawar, A.; Farswan, M.; Rathod, S. and Balaraman R. (2006). Modification of biochemical parameters of gentamicin nephrotoxicity by coenzyme Q10 and green tea in rats. Indian J Exp Biol.,44(5):416-8.
53. Emami, A.; Tofighi , A.; Rezayi ,S.A. and Gilani ,B.B. (2017). Effect of short-term coenzyme Q10 supplementation and pre-cooling on serum endogenous antioxidant enzymes of elite swimmers. J Strength Cond Res. doi: 10.1519/JSC.0000000000001971.
54. Shen,Q. and Pierce,J.D. (2015). Supplementation of coenzyme Q10 among patients with type 2 diabetes mellitus. Healthcare (Basel). 3(2): 296–309.
55. Noh, Y.H.; Kim, K,Y.; Shim, M.S.; Choi, S,H.; Choi, S.; Ellisman, M.H.; Weinreb, R.N.; Perkins, G.A. and Ju, W.K. (2013). Inhibition of oxidative stress by coenzyme Q10 increases mitochondrial mass and improves bioenergetic function in optic nerve head astrocytes. Cell Death Dis., 2013 Oct; 4(10): e820.
56. Lee, D.; Kim ,K.Y.; Shim, M.S.; Kim ,S.Y.; Ellisman, M.H.; Weinreb, R.N. and Ju, W.K.(2014). Coenzyme Q10 ameliorates oxidative stress and prevents mitochondrial alteration in ischemic retinal injury. Apoptosis,19(4):603-614.
57. Osborne, N.N.; Núñez-Álvarez, C.;Joglar, B. and Del Olmo-Aguado S.(2016). Glaucoma: Focus on mitochondria in relation

to pathogenesis and neuroprotection.Eur J Pharmacol. Sep 15; 787:127-33
58..