Renal Genomic Instability Induced by Aspartame and the Possible Influence of the Flaxseed Oil and Coenzyme Q10 in Male Rats

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Abstract: Aspartame (ASP) is one of the most widely artificial sweeteners consumed in various countries which added to a large variety of foods specially low calorie beverages. Flaxseed oil (FXO) is marketed as a nutritional supplement. It contains linolenic acid poly unsaturated fatty acid (omega-3- PUFA), that have antioxidant, anti-inflammatory effects and many beneficial health effects. Coenzyme Q10 (Co Q10) has gained considerable attention as a dietary supplement capable of influencing cellular bioenergetics, antioxidants and as a supplementary treatment for some chronic diseases. The present study is an effort aimed to investigate the possible protective influence of FXO and Co Q10 on renal genomic instability induced by aspartame. Adult male rats were divided into 4 groups (n=6), animals of group 1 (control) had free access to water and food materials. Group 2 (ASP) was daily administered orally Ad libitum drinking water containing 0.25 g/L aspartame. Group 3 (ASP+ FXO) was daily administered diet contains 15% FXO in combination with aspartame. Group 4 (ASP+ CoQ10) was daily administered diet contains 500 mg CQ10/kg diet in combination with aspartame till the end of the experiment after 60 days. Our results revealed that, oral administration of aspartame significantly increased serum urea, BUN, Creatinine, potassium levels and decreased sodium level. Also Our results showed that renal GSH level, GSH-Px, GSH-R, G6PDH, SOD activities and DNA, RNA, zinc content were significantly decreased. While the levels of H_2O_2, NO, TNF- α and percentage of DNA fragmentation were significantly increased comparing with normal control group. Oral administration of FXO and CoQ 10 along with aspartame ameliorated serum and renal alterations. Our data suggesting that the FXO and CoQ10 have the potential to protect against renal genomic instability and renal dysfunction induced by aspartame with the primary role for CoQ 10 that can restore all alterations to normal values.

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1. Introduction

Aspartame (L- aspartyl- L-phenylalanine methyl ester; ASP) is one of the most widely artificial sweeteners consumed in various countries which added to a large variety of foods specially low calorie beverages. The metabolism of ASP provides approximately 4 kcal/g of energy. However, this energy is negligible as the high intensity sweetening power of ASP (approximately 200 sweeter than sucrose by weight) means that little is needed to be added to foods to achieve sweetness **(Gougeon *et al.*, 2004; Magnuson *et al.*, 2007).**

Anecdotal reports have appeared in many literatures that suggest the oxidative stress induced by aspartame administration. On metabolism in humans and experimental animals, ASP is rapidly and completely metabolized to aspartic acid (40%), phenylalanine (50%) and methanol (10%). Methanol, a toxic metabolite is primarily metabolized by oxidation to formaldehyde and then to formate; these processes are accompanied by the formation of superoxide anion and hydrogen peroxide **(Parthasarathy *et al.*, 2006; Choudhary and Devi, 2014 a).**

Many publications recorded the genotoxic influence of ASP. **Rencuzogullari *et al.*, 2004** demonstrated chromosomal aberration, chromatide exchange and micronuclei in ASP treated- human lymphocytes. Additionally, **Belpoggi *et al.*, 2006** revealed that ASP increased incidence of malignant tumor-bearing animals, with an increase in lymphomas–leukemias, transitional cell carcinomas of the renal pelvis and ureter in female rats. Cumulatively, **Soffritti, *et al.*, 2010** recorded that ASP should be considered a carcinogenic agent causing hepatocellular carcinomas and adenomas in both male and female rats. Earlier studies have investigated that Asp induced hepatotoxic and nephrotoxic effects in rats **(Marielza *et al.*, 2007; Iman, 2011)**.

Worldwide nephrotoxicity possess a considerable health and economic burden. For this reason, search for strategies to prevent nephrotoxicity constitutes an active area of investigation. So a line of interest is the identification of renoprotective adjuvants for co-

administration along with potentially nephrotoxic agents **(Pabla and Dong, 2008)**

Currently, the increasing interest in the potential health benefits of plant compounds such as flaxseed is leading to greater daily consumption. Flaxseed oil (*Linum usitatissimum*), also known as linseed oil is widely used for its edible oil in many parts of the world. Nutritional recommendations have recently promoted the increased need to consume a-linolenic acid omega-3 polyunsaturated fatty acids (PUFAs) which present at high concentrations in flaxseed oil. Omega-3 may be beneficial for reducing inflammation as considered the key healing components (**He *et al.*, 2009; Houcine *et al.*, 2014).**

A number of investigations have demonstrated that diet supplemented with flaxseed oil has profound beneficial health effects in various pathologies. **Babu *et al.*, 2000** reported an increase in liver vitamin E of rats fed 10% flaxseed. Omega-3 PUFA was recorded as a potent anticarcinogen that can inhibit the growth and development of prostate cancer in the transgenic adenocarcinoma mouse prostate model and human breast cancer **(Chen *et al.*, 2002; Lin *et al.*, 2002).** As well as it can prevent azoxymethane-induced colon tumors in fisher male rats **(Williams *et al.*, 2008).** Earlier investigations have shown that flaxseed oil has antioxidant, hypolipidemic effects and prevents lead induced nephrotoxicity (**Newairy and Abdou, 2009; Abdel-Moniem, 2011**).

Recently, coenzyme Q10 (CoQ10; ubiquinone) has attracted a wide spread attention to its high bioavailability, low toxicity and antioxidant activity. Coenzyme Q10 belongs to a family of compounds that share a common structure, the benzoquinone ring, and differ in their isoprenoid lateral chain length. CoQ10 is a redox component of the mitochondrial respiratory chain. In eukaryotes, CoQ10 shuttles electrons from complexes I and II to complex III in the mitochondrial electron transfer system **(Quiles *et al.*, 2004; Marcoff and Thompson, 2007).**

CoQ 10 is produced in all tissues, cells and in the inner mitochondrial membrane. Approximately half of the body's CoQ 10 is obtained through dietary fat ingestion, whereas the remainder results from endogenous synthesis in most mammalian cells and organs **(Bravo *et al.*, 2012)**. CoQ10 levels in membranes are regulated through the mevalonate pathway and by physiological factors that are related to oxidative activity of the organism. Evidence that the increase in CoQ content occurred after the increase in metabolic rate and free radical production **(Ernster and Dallner, 1995; Bookstaver *et al.*, 2012**).

The reduced form of CoQ10 (ubiquinol) is believed to be a powerful lipophilic antioxidant that participates in tocopherol and ascorbate recycling as antioxidants, thus protecting lipids from peroxidation **(Bentinger *et al.*, 2007; Wyman *et al.*, 2010; Jiménez-Santos *et al.*, 2014).**

Inclusion of CoQ10 in the diet in various studies has shown that, CoQ provides some protection against cardiotoxicity or liver toxicity during cancer treatment (**Roffe *et al.*, 2004**). Likewise, the results of **Quiles *et al.*, 2004** suggest that a long-term supplementation with a small dosage of coenzyme Q10 protects from age-related DNA double-strand breaks might represent a good anti-aging therapy in rats fed on a PUFA-based diet**.** Additionally, **Yenilmez *et al.*, 2010** recorded that CoQ10 treatment appeared to ameliorate the Ochratoxin A-induced renal damage**.** Moreover, **Jiménez-Santos *et al.*, 2014** provide that, CoQ10 supplementation improves metabolic parameters, liver function and mitochondrial respiration in rats with high doses of atorvastatin and a cholesterol-rich diet.

Therefore, the present study is an effort aimed to investigate the possible protective influence of FXO and Co Q10 on renal genomic instability induced by aspartame.

2. Material and methods

1-Expermental material

Diet sweet (Aspartame, 20 mg) was purchased from Amriya pharmaceutical industries, Alexandria, Egypt.

Flaxseed oil was obtained from local market of Herbs and Medicinal plants, Cairo, Egypt.

Co-enzyme Q10 (ubiquinone, 30 mg) was obtained from MEPACO Pharmaceutical Company, Egypt**.**

2- Animals and treatment schedule

Adult male Wistar albino rats weighing 120-180 g were used as experimental animals. The animals were obtained from Animal House in Faculty of Vet. Medicine, Zagazig University, Egypt. They were maintained on stock diet and kept under fixed appropriate conditions of housing and handling. The experiment was followed the recommendations of the National Institutes of Guide for Care and Use of Laboratory Animals (**Institute of Laboratory Animal Resources, 1996).**

The animals were divided into 4 groups; each group consisted of six rats. Animals of group 1 (control) had free access to water and food materials. Group 2 (ASP) was daily administered orally ad lib drinking water containing 0.25 g/L aspartame (**Collison *et al.*, 2012**). Group 3 (ASP+ FXO) was daily administered diet contains 15% flaxseed oil (**Lawrenz et al, 2012)** in combination with aspartame. Group 4 (ASP+ CoQ10) was daily administered diet contains 500 mg CQ10/kg diet **(Ibrahim *et al.*, 2000)** along with aspartame.

3-Handling of blood and tissue samples

At the end of the experimental period (60 days), the animals were sacrificed after being fasted. Blood

samples were collected and centrifuged for 10 min at 5000 rpm to obtain clear serum which were stored at −20 ◦ C for different analysis. For DNA and RNA extraction, sample from kidney was removed, rinsed with ice-cold saline solution, and directly frozen by dropping into liquid nitrogen then stored at -80 °C for further study. As well as, part of kidney homogenized in cold potassium phosphate buffer (0.05 M, pH 7.4). The homogenates were centrifuged at 5000 rpm for 10 min at 4◦ C. The resulting supernatant was used for different analysis.

1.3-Assessment of kidney function tests

Measurement of serum urea and creatinine levels were carried out according to **(Fawcett and Soctt, 1960; Schirmeister, 1964)** respectively using colorimetric assay kits according to the recommendations of the manufacturer (Biodiagnostic-Egypt).

2.3-Assay of serum and renal electrolytes

Serum sodium and potassium concentrations were analyzed according to **(Trinder, 1951; Sunderman and Sunderman, 1958)** respectively.

Concerning zinc, Parts of the renal cortical tissue were dried overnight at 80 ◦ C and the dry weight was recorded. The samples were digested with equal volumes of 30% (w/v) H_2 O_2 and 70% (w/v) nitric acid, and the clear digest was diluted with ultrapure water (1:3). Renal zinc ion concentrations was analyzed according to **(Hayakawa and Jap, 1961)** following the manufacturer's instructions (Biodiagnostic, Egypt).

3.3-Determination of renal oxidative stress markers

Assessment of reduced glutathione (GSH) levels, activities of glutathione peroxidase (GSH-Px), glutathione reductase (GSH-R) and glucose 6-phosphate dehydrogenase (G6PDH) were done according to **(Beutler *et al.,* 1963**, **Paglia and Valentine, 1967; Goldberg and Spooner, 1983; Kornberg and Horecker, 1955)** respectively.

The level of nitric oxide (NO) and hydrogen peroxide were measured according to **(Montgomery and Dymock, 1961; Aebi, 1984)** respectively according to the manufacturer's instructions (Biodiagnostic, Egypt).

The level of pro-inflammatory cytokine tumor necrosis factor- alpha (TNF- α) in renal homogenates was determined by aid of ELISA using rat TNF- α immunoassay kit according to the recommendations of the manufacturer.

4.3-Molecular-Genetic Studies

1.4.3-Determination of renal nucleic acid concentrations.

Renal DNA extraction and quantification were done according to **(Laird *et al.,* 1991; Perandones *et al.,* 1993; Stamm and Berka, 2006).** While RNA extraction and quantification were done by using TRIzol reagent according to **(Chomczynski and Sacchi, 1987).**

2.4.3-Evaluation of DNA fragmentation (%) by DPA assay

The percentage of DNA fragmentation was used as indicator for oxidative DNA damage using DPA assay. The latter was conducted using the procedure of **(Perandones *et al.,* 1993).**

4-Statistical Analysis

Results are expressed as mean ± S.E. Data were analyzed using one-way analysis of variance (ANOVA). All statistical tests were done by using (SPSS Software, version 22, SPSS Inc., Chicago, USA) and the differences were considered significant at $P< 0.05$.

3. Results

The results of the current study revealed that oral ASP administration caused marked renal dysfunction as evidenced by the significant ($P< 0.05$) increase in serum urea, BUN, creatinine and potassium levels along with a significant depletion in serum sodium and renal zinc levels (**Table 1**).

Our data confirmed marked significant ($P< 0.05$) reduction in renal GSH level, GSH-Px, GSH-R, G6PDH, and SOD activities **(Table 2)** along with elevation in H_2O_2, NO and TNF- α levels (**Table 3**). These were accompanied by reduction in DNA and RNA content with increase in the percentage of DNA fragmentation (**Table 3)** in ASP- treated rats than normal control group.

Table 1. Effect of flaxseed oil and Coenzyme Q10 treatment on serum urea, BUN, creatinine (mg/dl), sodium, potassium (mmol/L) and renal zinc (µg/ mg tissue) in aspartame treated rats.

	Control	ASP	ASP+FXO	ASP+CoQ10
Urea (mg/dl)	28.17±1.56*	60.50±2.57†	31.50±2.51*	28.67±2.40*
BUN (mg/dl)	13.13±0.73*	28.19±1.20†	14.68±1.17*	13.36±1.12*
Creatinine (mg/dl)	0.66±0.05*	1.75±0.08†	1.08±0.05$^{\neq}$	0.83±0.04*
Sodium(mmol/L)	148.67±3.99*	113.33±2.97†	128.67±1.15$^{\neq}$	144.83±5.09*
Potassium (mmol/L)	3.90±0.20*	5.82±0.50†	4.63±0.19*	4.38±0.27*
Zinc (µg/ mg tissue)	54.67±3.70*	29.83±1.90†	44.00±2.08$^{\neq}$	50.83±2.50$^{*\neq}$

Data are expressed as means± S.E. Data having different superscript are significant at $P < 0.05$.

Table 2. Effect of flaxseed oil and Coenzyme Q10 treatment on renal GSH content (mg/ gm tissue), GSH-px, GSH-R, G6PDH and SOD activity (U/ gm tissue) in aspartame treated rats.

	Control	ASP	ASP+FXO	ASP+CoQ10
GSH (mg/ gm tissue)	37.83±2.46*	19.50±1.12†	29.83±1.01$^{\neq}$	36.00±1.46*
GSH-px (U/ gm tissue)	109.33±4.34*	64.67±3.31†	87.83 ±2.64$^{\neq}$	104.17±4.54*
GSH-R (U/ gm tissue)	36.33±2.44*	21.17 ±1.72†	29.16 ±1.40$^{\neq}$	36.00±2.07*
G6PDH (U/ gm tissue)	6.12±0.21*	2.87±0.19†	4.73±0.27$^{\neq}$	5.27±0.33$^{\neq}$
SOD (U/ gm tissue)	7.08±0.32*	3.03±0.17†	6.00±0.42$^{\neq}$	6.23±0.33$^{*\neq}$

Data are expressed as means± S.E. Data having different superscript are significant at $P < 0.05$.

Table 3. Effect of flaxseed oil and Coenzyme Q10 treatment on renal H2O2, NO (µmol/gm tissue), TNF- α (pg/ 100mg tissue), DNA, RNA content (µg/ mg tissue) and DNA fragmentation (%) in aspartame treated rats.

	Control	ASP	ASP+FXO	ASP+CoQ10
H2O2(µmol/gm tissue)	1.29±0.08*	2.73±0.15†	2.02±0.12$^{\neq}$	1.49± 0.10*
NO (µmol/ gm tissue)	123.50±3.11*	161.00±4.40†	129.67±4.64*	123.83±4.20*
TNF- α (pg/100mg tissue)	91.00±7.62*	320.00±31.71†	168.33±10.38$^{\neq}$	105.67±3.94*
DNA (µg/ mg tissue)	2.24±0.08*	1.09±0.06†	1.71±0.10$^{\neq}$	2.11±0.06*
RNA (µg/ mg tissue)	1.74±0.07*	0.93±0.04†	1.36±0.06$^{\neq}$	1.64±0.04*
DNA fragmentation (%)	26.17±2.91*	69.33±4.69†	44.17±2.98$^{\neq}$	33.00±3.25*

Data are expressed as means± S.E. Data having different superscript are significant at $P < 0.05$.

It is obvious from the present study that oral administration of FXO to ASP-treated rats improved and reduced aspartame side effects on kidney tissues. FXO was significantly ($P < 0.05$) increased serum sodium, renal GSH level, GSH-Px, GSH-R, G6PDH activities and DNA, RNA content along with reduction in H2O2, TNF- α and the percentage of DNA fragmentation comparing with ASP- treated rats. Also, FXO can restore serum urea, BUN, potassium and renal NO to normal values.

In our experiment, oral administration of CoQ10 reduced aspartame side effects on kidney tissues and can restore all alterations toward normal values.

Discussion

Worldwide nephrotoxicity poses a considerable health and economic burden. For this reason, a line of interest is the identification of the antioxidants and nephroprotective agents.

There is a great interest in the development of oxidative stress from oral aspartame administration.

In the present study, oral ASP administration caused marked renal dysfunction as evidenced by the significant increase in serum urea, BUN, creatinine and potassium levels along with a significant depletion in serum sodium level. Lower value of serum sodium indicated inability of kidney to conserve sodium. While, elevation in serum Potassium may be due to reduced its excretion that aggravated by leakage of intracellular potassium into blood stream as a result of methanol metabolite of aspartame induced lesions in renal tubular epithelium **(Choudhary and Devi, 2014 b).**

Our data confirmed marked significant ($P< 0.05$) reduction in renal zinc, GSH levels, GSH-Px, GSH-R, G6PDH, and SOD activities along with elevation in H_2O_2, NO and TNF- α levels. These were accompanied by reduction in DNA and RNA content with increase in the percentage of DNA fragmentation in ASP- treated rats than normal control group. These results are in agreement with those of (**Parthasarathy *et al.*, 2006; Choudhary and Devi, 2014 a)** whom demonstrated that, the alteration in the free radical scavenging enzymes in the aspartame administered animals clearly indicates that superoxide anion and hydrogen peroxide generation may be due to the methanol production from aspartame which further converted to formaldehyde. This can provide an explanation for the observed decrease in GSH content that be caused by its rapid reaction with the highly reactive compound, formaldehyde. In addition, methanol administration caused a decrease in the enzymatic antioxidant (SOD and CAT) in the lymphoid organs.

Interestingly, (**Zeng *et al.*, 2003; Zararsiz *et al.*, 2007; Duong *et al.*, 2011)** mentioned that both the induction of oxidative stress and suppression of antioxidant enzymes by formaldehyde has been demonstrated in kidney tissues. These antioxidant enzymes protect cells against oxidative damage and a change in their activity levels may indicate the level of oxidative damage in target tissues and/or cells. Normally, the antioxidant enzymes CAT and GSH-Px protect SOD against inactivation by H_2O_2. Reciprocally, SOD protects CAT and GSH-Px against superoxide anion. However, over load of free radical could have been upset these regulations.

The highly reactive free radicals generated during the course of the reaction are detoxified by GSH and/or by the end electron acceptor NADPH produced by the G6PDH enzyme, thereby over production of H2O2 may inhibit G6PDH and GSH- R

(Kurutas and Tuncer, 2000; El-Nekeety *et al.,* 2009).

Currently in our study, aspartame increased the production of nitric oxide in kidney tissues. These results are in favoring of the possibility that over-production of NO plays an important role in the pathogenesis of kidney damage. As infiltrated macrophages release reactive oxygen species and large quantities of nitric oxide (NO), via inducible NO synthase (iNOS)-dependent mechanism in response to inflammatory stimuli **(Harstad and Klaassen, 2002).**

Based on this, excess NO reacts with superoxide anion to generate peroxynitrite radical that causes further cell damage by oxidizing and nitrating cellular macromolecules. Also, excess NO depletes intracellular GSH increasing the susceptibility to oxidative stress (**Jung *et al.,* 2009).**

In speculating about parallel changes in antioxidant activities and cytokine production. Our results confirmed that as the level of TNF- α in the kidney was significantly increased indicating the severity of the oxidative stress-induced by aspartame.

Tumor necrosis factor alpha (TNF- α) is a pleiotropic cytokine produced by a variety of cell types including macrophages, T-cells, mast cells, and keratinocytes. Leukocyte infiltration, a hallmark of inflammation is observed in most liver injuries caused by various types of chemical substances **(Luster, 2001**).

Reactive oxygen species (ROS) have been implicated in the development of genomic instability. In our experiment, it was observed that aspartame-induced fragmentation of genomic DNA and decrease in DNA, RNA content. These results can possibly indicate the failure of DNA repair mechanisms.

Many authors described the mechanism through which aspartame could induce DNA fragmentation and chromosomal aberrations. **Abhilash *et al.,* 2011** mentioned that a small amount of aspartame significantly increased the plasma methanol levels that associated with increased levels of free radicals production inducing DNA damage and subsequently leading to formation of chromosomal aberrations.

Oxidative stress had contributed to losing of mitochondrial membrane integrity and became hyper-permeable with more transition pore opening, matrix swelling, outer membrane lysis that potentiate the release of apoptosis-inducing factor and endonuclease G from the mitochondria. The released endonucleases pass to the nuclei and enhance the fragmentation of the nuclear DNA (**Masubuchi *et al.,* 2005; Bajt *et al.,* 2006).** Additionally, the genotoxic potential of ASP has been observed by **(Alleva *et al.,* 2011)** who stated that ASP is a potential angiogenic agent that can induce ROS production that stimulate induction of cytokines, growth factors, interleukin 6 and vascular endothelial growth factor and their soluble receptors release from the endothelial cells. Cumulatively, data in the present study demonstrate the ability of aspartame to rapidly elevate nucleic acid oxidation and activate apoptotic processes and oxidative damage in kidney cells.

It is obvious from the present study that oral administration of FXO to ASP-treated rats improved and reduced aspartame side effects on kidney tissues. FXO was significantly ($P < 0.05$) increased serum sodium, renal GSH level, GSH-Px, GSH-R, G6PDH activities and DNA, RNA content along with reduction in H2O2, TNF- α and the percentage of DNA fragmentation comparing with ASP- treated rats. Also, FXO can restore serum urea, BUN, potassium and renal NO to normal values.

There is a continuous search for agents that provide nephroprotection against nephrotoxic agents. During the past decade interest in omega-3 PUFAs which may be beneficial for reducing inflammation (**He *et al.,* 2009).** This could be attributed to the fact that FXO might have ameliorating the renal damage caused by aspartame in two possible ways: First, FXO supplementation increases the levels of SOD, catalase and GSH-Px in the proximal tubular epithelial cells resulting in enhanced defense against ROS. Second, the constituent omega-3 PUFA of dietary FXO may have replaced the polyunsaturated fatty acid components of the brush border membrane that had been attacked by oxygen free radicals **(Masters, 1996; Ozgocmen *et al.,* 2000).**

An additional explanation for the observed nephroprotective activities in FXO fed rats. **Cohen *et al.,* 2005** stated that FXO appears to accelerate repair and/or regeneration of injured organelles e.g., mitochondria, lysosomes and plasma membrane.

Flaxseed oil significantly reduced NO, this can be suggested that the active flaxseed peptide fractions may have altered the pathway for NO synthesis in the macrophages. As well as, PUFA has shown that the activity of potential therapeutic agents of flaxseed oil is responsible for the inhibition of NO production and subsequent inhibition of iNOS mRNA and protein expressions in macrophage **(Ho and Lin, 2008; Pan *et al.,* 2008).** Moreover, **Hu *et al.,* 2007** found that flaxseed plant lignans exhibited strong antioxidant and protective effects in quenching the free radical and inhibiting peroxyl-radical-mediated damage of plasmid DNA and phosphatidylcholine liposomes at potentially feasible physiological concentrations.

Zinc acts as a cofactor for SOD, preserve GSH and induce metallothionein which have antioxidant and metal-chelating properties **(Rooney, 2007).** Zinc is involved in genetic stability and gene expression in a variety of ways as DNA repair, reduction of DNA fragmentation. The structural role of zinc (II) ions is

accentuated in the stabilization of zinc finger motif that have high affinity to DNA. Thus, zinc play important roles in the regulation of transcription in the cellular metabolic network **(Bussereau *et al.*, 2004; Talevi *et al.*, 2013; Nejdl *et al.*, 2014).**

On the basis of these results, FXO plays high protective action as antioxidant and antimutagenic agent.

Recently, coenzyme Q10 has attracted a wide spread attention to its high bioavailability, low toxicity and antioxidant activity. In our experiment, oral administration of CoQ10 reduced aspartame side effects on kidney tissues and can restore all alterations toward normal values.

The well-recognized function of CoQ10 is antioxidant, which protects the cells both directly by preventing lipid peroxidation and indirectly by regenerating other antioxidants such as ascorbate and α-tocopherol. In the plasma membrane, CoQ10 functions in the transmembrane electron transport to stabilize extracellular ascorbate **(Quiles *et al.*, 2004; Marcoff and Thompson, 2007).**

Many authors recorded the powerful antioxidant activity of CoQ10. **Sohet *et al.*, 2009** investigated that CoQ10 suppresses the generation of reactive oxygen species by blunting the expression of NADPH oxidase. Additionally, **Lee *et al.*, 2012** stated that CoQ10 may assist SOD in the uptake of superoxide radical to form oxygen and hydrogen peroxide**.** As well as, the significant negative correlation was seemed between the ratio of 8-OHdG/dG and ubiquinol-10/ubiquinone-10 **(Kaya *et al.*, 2012)**.

In relation with the possible role of CoQ in the preservation of DNA from oxidative damage, it has been reported that CoQ increases DNA repair rate probably due to an inhibition of additional damage by protecting the cells against further oxidation and that such effect is likely ascribed to the known antioxidant activity of CoQ **(Tomasetti *et al.*, 2001).** Immunohistochemical analysis revealed that coenzyme Q10 has anti-inflammatory properties. Another hypothesis is that the nephron-protective effect of CoQ10 can be attributed to its ability to inhibit the activation of NF-KB signaling pathway which promotes the transcription of NADPH oxidase, TNF- α and iNOS genes thus suppresses excess NO production (**Takaya *et al.*, 2006; Morishima *et al.*, 2009).** Also many studies showed improvement in the endothelial relaxation and antihypertensive effect with coenzyme Q10 administration. This might be related to its capability of enhancing endothelial function by counteracting nitric oxide oxidation and inducing vasodilation via decreased peripheral resistance in the vasculature **(Rosenfeldt *et al.*, 2007; Belardinelli *et al.*, 2008).** These authors hypothesized that the enrichment of cells with CoQ10 yielded an ordering and condensing effect on cell membranes, and thus may have restricted the number of radicals capable of reaching the cells' DNA. Thus CoQ10 has the potential to protect against renal genomic instability and renal dysfunction induced by aspartame.

Conclusion

To conclude, the present study demonstrated that aspartame elicited deleterious nephrotoxic effects. FXO by virtue of its intrinsic biochemical and antioxidant properties prevented aspartame-induced nephrotoxicity by empowering antioxidant defense mechanism thereby reducing genomic instability and oxidative damage. This effect was found to be similar or less to the protective effects of CoQ10 due to its antioxidant and/or anti inflammatory properties.

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