IOSR Journal Of Pharmacy And Biological Sciences (IOSR-JPBS)
e-ISSN:2278-3008, p-ISSN:2319-7676. Volume 14, Issue 1 Ser. IV (Jan – Feb 2019), PP 73-82
www.Iosrjournals.Org

Adaptogenic neuronal activity of *ficus carica* and ubiquinone on neuron-toxicity and oxidative stress in lithium carbonate treated rats

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Abstract: *Lithium carbonate (LC) is the most prevalent used as anti-psychological drug and can curbing reproductive performance via testicular toxicity and induction of oxidative stress. This study aimed to investigate examines the neuromodulatory effects of Ficus carica leaves extract and ubiquinone (Coq10) against lithium carbonate induced neuron-toxicity and oxidative stress in male rats. So forty two (42) rats were assigned into 7 groups of six animals each. The 1st group was control (C) received distill water. The 2nd groups treated with extract 200 mg /kg body weight Ficus carica extract (FE). The 3rd groups treated with 20 mg /kg b.w of CoQ10 (CoQ10). The 4th group treated with lithium carbonate (25 mg /kg b.w) (LC). The 5th group treated with LC+ FE (LC+ FC) 25 mg /kg body weight of Lithium carbonate and 200mg/kg b.w of FE. The 6th group treated with LC 25 mg /kg body + CoQ10 20 mg/kg b.w (LC+ CoQ10). The 7th group treated with LC 25 mg /kg body weight + FE (200mg/kg b.w) + CoQ10 20 mg/kg b.w (LC + FC +CoQ10). The experiment lasted for 60 days. The data revealed that LC induces significant (P>0.05) increase in serum 5HT, GSSG, MDA, MPO, PGE2, IL-1 β and IL-6. But showed significant (P>0.05) decrease in 5HIAA, ACHE, BDNF, serum GSH. From another side, FC, CoQ10 and their combination improve negative impacts exhibited by LC. On the whole, Obtained data concluded that LC acts as a bipolar treatment but increase neuro toxicity through increase oxidative stress markers and inflammatory cytokines. Alternatively, FC, CoQ10 and their combination improve negative impacts of LC and can normalize bipolar symptoms.*

Keywords: *ficus carica, ubiquinone, lithium carbonate, oxidative stress and Neuromodulatory*

Date of Submission: 01-02-2019 Date of acceptance:18-02-2019

I. Introduction

Ficus carica leaves are one of the oldest plants has conventionally been used for cardiovascular, antispasmodic, metabolic, respiratory, reproductive disorders and anti-inflammatory (Vikas et al., 2010). It contains minerals, high vitamins, and phenolic contents that play a very important role in its antioxidant capacity (Veberic et al., 2008)**.** Analysis of antioxidants in fig revealed that it contains large amounts of antioxidantsvitamins; vitamin A and vitamin C. Lattanzio, (2003) reported that In addition to antioxidant effects, phenolic compounds have a wide range of biochemical properties and can also have a beneficial effect in preventing the development of diseases such as cancer and cardiovascular diseases. There is linear correlation between total phenolic content and the antioxidant capacity (Cai et al., 2004; kumaran and karunakaran, 2006).

Ubiquinone also is called a coenzyme10 (CoQ10) that is widespread in the bodies of most animals (Mancini et al., 1998). Also, it is ingredient of the electron transport chain and takes part in aerobic cellular respirations, which produce energy in form ATP. CoQ10 is an antioxidant, composite of the respiratory chain. Many studies have been investigating the Coq10 supplements for male infertility as antioxidants to improve sperm parameters (Safarinejad et al., 2012). In mitochondrial, CoQ10 is concentrated, which it is play a role in energy production. It also considered as an antioxidant, preventing lipid peroxidation of the membranes of sperm. Recent research indicated that CoQ10 improve the quality of semen in males with Infertility (Lewin and Lavon, 1997). Furthermore, Ernster and Dallner (1995), Bhagavan and Chopra (2006**)** stated that ubiquinone is a benzoquinone soluble lipid- which is an essential ingredient of the respiratory chain in mitochondrial to synthesize adenosine triphosphate. Statins can reduce the synthesis of cholesterol and other downstream molecules of mevalonate. Mevalonate is an introduction of coenzyme Q10. Statins not only lower the

cholesterol but also lower the level of Q10 enzyme (Folkers et al., 1990), (Chu et al., 2006). Higher levels of oxidation and inflammation play a role in the development of coronary artery disease (Harrison et al., 2003), (Siegel et al., 2013). Coenzyme Q10 is an intracellular antioxidant that protects the membrane phospholipids, mitochondrial membrane protein, and LDLC from Free radicals caused by oxidation damage (Alleva et al., 1995), (Singh et al., 2007).

Lithium carbonate is a very invaluable and widely used drug for several treatment psychiatric disorders. (Xu et al., 3003), (Gupta et al., 1995) However, prolonged treatment with therapeutic levels of lithium (Li) causes toxic side effects (Thakur et al., 2003). Besides this, permanent neurological diseases, hepatic, renal and cardiac damage have been reported as a result of Li intoxication. (Frassati et al., 2004), (Simard et al., 1989) It has been suggested that oxidative stress, one of the major toxic effects of Li, leads to increased lipid peroxidation in the cerebral cortex and kidney.(Sawas and Gilbert 1985)

Increase amount of Li cause toxic effects in many organs such as testicular, (Thakur et al., 2003) heart, (Frassati et al., 2004) brain (Simard et al., 1989) and kidney. (Sawas and Gilbert 1985). These studies suggest that the possibility that the respiratory system **may** also be affected by Li via the systemic circulation.

This study was conducted mainly to examine the neuromodulatory effects of Ficus carica leaves extract and ubiquinone (Coq10) against lithium carbonate-induced toxicity neurons and oxidative stress in male rats.

II. Materials and methods

1.1. Experimental animals:

Male albino rats weighted from 180 to 200 g obtained from the animal house of NODCAR, Giza, Egypt. The rats were housed in wire mesh cages under standard conditions (temperature 25 - 28o C, 12h light and 12h darkness cycles). Animals were fed ad libitum with pelleted standard rat diet and free water.

1.2. Extract preparation:

Almost 2 kg of Ficus carica leaves soaked in ten volume of ethanol 70% and placed in a clean, flat glass container. Then extraction implemented using ultrasonic for 40 min. Then filtrated the content by cotton material. The extract then was filtered through filter paper (Whatman) and dried by electric oven at 450C temperature and continued up to obtain ethanol (205 g) extract. The extract was stored in an air tight container.

1.3. Experimental design

Forty two (42) rats were divided into 7 groups of six animals each. The 1st group was control (C). The 2nd groups treated with extract 200 mg /kg body weight (FE). The 3rd groups treated with 20 mg /kg b.w of CoQ10 (CoQ10). The 4th group treated with lithium carbonate (25 mg /kg b.w) (LC). The 5th group treated with LC+ FE (LC+ FC). The 6th group treated with LC+ CoQ10 (LC+ CoQ10). The 7th group treated with LC+ FE + CoQ10 (LC + FC +CoQ10). All treatments were given p.o via oral intubation and the experiment duration maintained for 60 days.

1.4. Tissues collection

Brain cortex samples were taken at sacrificing period from 6 rats from each group. Then separate the brain, homogenized with an ice jacket plus 10% potassium chloride in a dilution 10% of tissue homogenate, then centrifugation at 5000 rpm under cooling for 20 min. at 4 ◦C. The homogenates were used for the determination of serotonin (5-hydroxytryptamine) (5HT), 5HIAA, Acetylcholinesterase (ACHE), Brain-derived neurotrophic factor (BDNF), reduced glutathione, (GSH), oxidised glutathione (GSSG), Serum malondialdehyde (MDA), MPO, prostaglandin E2 (PGE2), serum interleukin 1 beta (IL-1 β) and serum interleukin 6 (IL-6).

1.5. Determination of tissue 5HT and 5HIAA (µg /g tissue) levels by HPLC:

For monoamines determination, the sample was immediately extracted from the trace elements and lipids by solid phase extraction NH2 phase (CHROMABOND column cat. No.730031). column was AQUA 150 mm C18, 5µ. (Phenomenex, USA): mobile phase phosphate buffer (20mM potassium phosphate), pH 2.7, flow rate was 1.5 ml/min, wave length 290 nm (Pagel et al., 2000).

1.6. Determination of Acetylcholinesterase (AChE) activity in brain tissue homogenate:

The procedure used for the determination of AChE activity in hippocampus tissue is a modified Ellman method according to Gorun et al. (1978). AChE activity was determined after extraction using following protocol: The brain hippocampus tissue samples were weighed and homogenized in a 20-mmol-phosphate buffer, pH 7.6 (5 % w/v). 0.14-ml of phosphate buffer consisted of 20 mmol potassium dihydrogen phosphate (pH 7.6), 0.05 ml of 5-mmol-acetylthiocholine iodide and 0.01 ml of sample. Incubate 10 min at 38 °C, the reaction was stopped with DTNB – phosphate ethanol reagent (1.8 ml). Wave length was 412 nm using Shimadzu spectrophotometer

UV –2425. Omitting the enzyme from the incubation mixture made the control samples. After adding reagent color, appropriate amount of tissue homogenates or serum was added to the control.
The cholinesterase activity was determined as µmol SH from a standard curve.

1.7. Determination of brain-derived neurotrophic factor (BDNF) in the brain (mg/g tissue)

BDNF levels were estimated using a rat-specific immunoassay kit (Rat BDNF ELISA) from Glory Science, as described in manufacturer's protocol. The intensity of the colored product was directly proportional to the concentration of rat BDNF, as determined using a micro plate reader (Biotech ELx800) set at 450 nm. The sample concentration was determined against a standard curve.

1.8. Determination of tissue GSH (µmol /g tissue) and GSSG (µmol/g tissue) levels by HPLC:

GSH and GSSG were detected by HPLC system with column µBondapak 30 cm × 3.9 mm C18. Flow rate: 1ml/min and wavelength was 190 nm. Ingredient of mobile phase is 0.0025 M sodium phosphate, pH 3.5, containing 0.005 M tetrabutylammonium phosphate and methanol 3% . (Jayatilleke and Shaw, 1993).

1.9. Determination of tissue MDA (nmol/g tissue) by HPLC:

Column was Supelcosil C18 (5 µm) 250 x 4.6. Ingredient of mobile phase is 30 mmol phosphate buffers (pH 3.6): methanol (82.5:17.5 v/v). Flow rate was 1.2 ml/min; wavelength was 250 nm. (Karatepe , 2004).

1.10. Determination of brain IL-1β, IL-6, PGE2 and MPO levels were determined by ELISA kit (RayBio ® Rat IL-1 beta USA) and according to manufacturer's instructions.

1.11. Statistical analysis

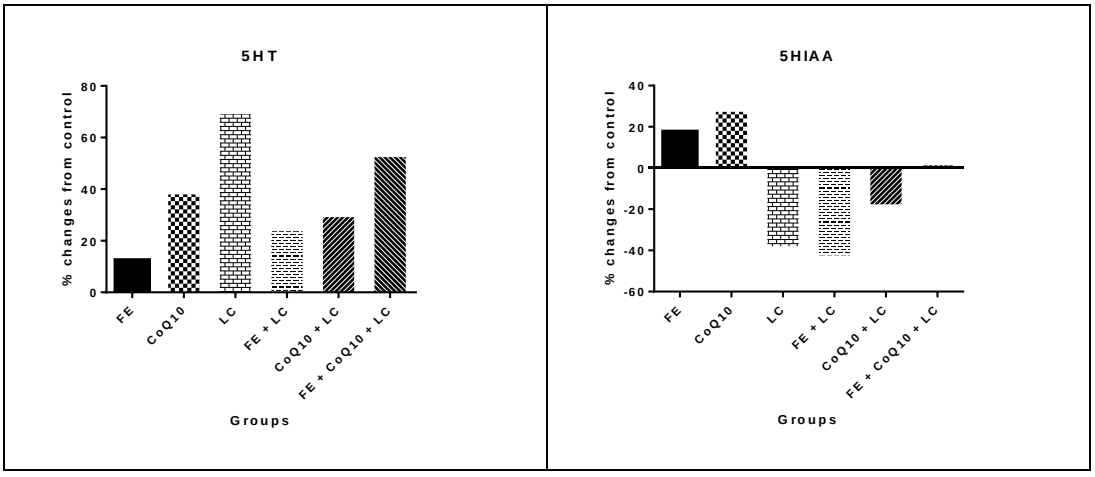
All values were explained as means ± SEM. Using one-way ANOVA test we make a comparisons between means, followed by Duncan's multiple comparisons test. The level of significance was set at $p < 0.05$. SAS was used for all statistical analysis data.

III. Results and discussion

Table 1: Prophylactic effects of FC, Coq10 and their combination on brain oxidative neurotransmitters and neurotrophic factors (5HT, 5HIAA, AChE and BDNF) in rats treated with LC

Groups	Parameters			
	5HT	5HIAA	AChE	BDNF
Control	0.454 ± 0.041	0.358 ± 0.033	4.93 ± 0.47	42.81 ± 2.49
FE	0.511 ± 0.049[a]	0.422 ± 0.033[a]	5.65 ± 0.39[a]	49.94 ± 2.88[a]
CoQ10	0.651 ± 0.059[a]	0.476 ± 0.048[a]	5.10 ± 0.35	45.58 ± 2.02[a]
LC	0.908 ± 0.043[a]	0.174 ± 0.013[a]	3.48 ± 0.19[a]	28.38 ± 1.39[a]
FE + LC	0.675 ± 0.030[ab]	0.283 ± 0.016[ab]	4.56 ± 0.27[b]	39.73 ± 2.01[b]
CoQ10 + LC	0.655 ± 0.034[ab]	0.306 ± 0.016[b]	3.68 ± 0.35[a]	35.07 ± 1.67[ab]
FE + CoQ10 + LC	0.801 ± 0.048[ab]	0.364 ± 0.035[b]	4.62 ± 0.34[b]	40.15 ± 2.50[b]

Data are expressed as Mean ± S.E.M for 6 rats /group.
a significant difference from control group at the same column with one way ANOVA at P < 0.05.
b significant difference from L at the same column with one way ANOVA at P < 0.05.



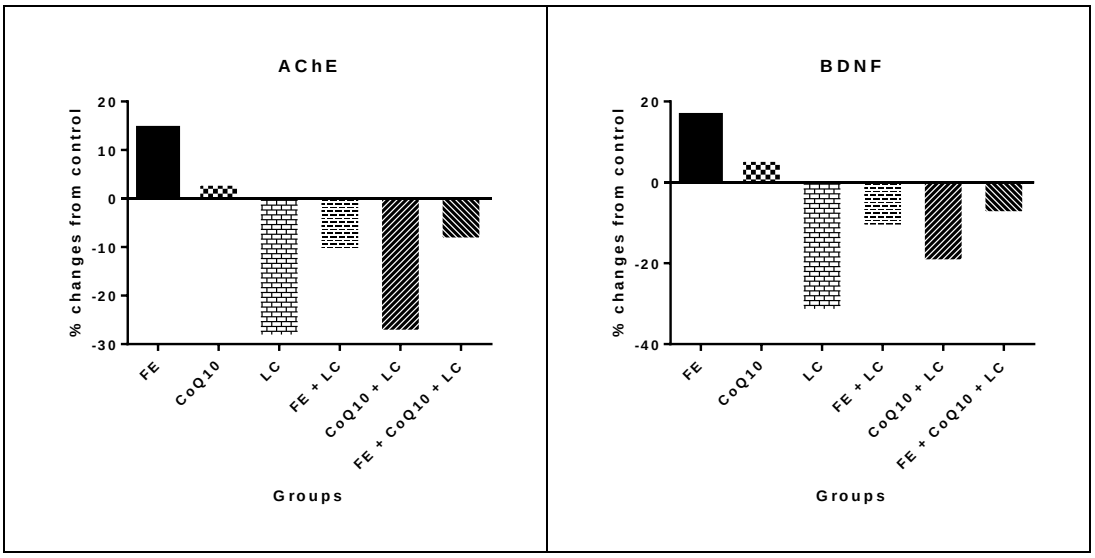


Figure 1: % changes from control of FC, Coq10 and their combination on brain oxidative neurotransmitters and neurotrophic factors (5HT, 5HIAA, AChE and BDNF) in rats treated with LC.

Results in Table (1) showed FC, Coq10 and their combination effects on brain (5HT) in rats treated with LC, these data illustrated that the highest value in 5HT recorded by LC group (0.908) followed by FE + CoQ10 + LC group (0.801), in another side no significant difference between groups (CoQ10, CoQ10 + LC and FE + LC) in 5HT content (0.651, 0.655 and 0.675), respectively. From another side, FE group have the lowest value in 5HT content (0.511) when compared with all groups may be lead to the protection offered by FE against chemo convulsions in animals.

The results are graphically illustrated in figure (1) showed % changes from control of FC, Coq10 and their combination on brain serotonin (5HT) in rats treated with LC. The FE group recorded a significant decrease in the levels of serotonin to 13.3 % when compared to the normal control levels, followed by CoQ10, and CoQ10 + LC groups both of them recorded (44.4%) as showed in Fig. (1). Then FE + LC group recorded 48.9% percentage in change from control in 5HT level. From another side the LC group increased on the serotonin change up to (100 %) compared to the normal control values.

Also, results in table (1) explained the value of 5HIAA in rat brain, from these data the content of 5HIAA ranged from 0.174 to 0.476 in groups LC and Coq10, respectively. The changes percentage from control of FC, Coq10 and their combination on 5HIAA brain in rats treated with LC illustrated in Fig. (1) we found CoQ10 group recorded (34.3%), followed by FE group (20.0%), then FE + CoQ10 + LC group (2.9%), CoQ10 + LC group (-14.3%), FE + LC group (-20.0%), finally LC group (-51.4%).

In addition, results in table (1) showed Acetylcholinesterase (ACHE) levels in all groups, from results we found significant difference from control group at the same column with one way ANOVA at $P < 0.05$ in groups FE, LC and CoQ10 + LC, while groups FE + LC and FE + CoQ10 + LC have a significant difference from L at the same column with one way ANOVA at $P < 0.05$. LC group recorded the lowest value of ACHE (3.48), while the FE group has the highest value (5.65). Also, Fig. (1) showed the biggest change percentage from control in AChE content in rats treated with LC appeared by FE group (14.6%), on the other hand the smallest change percentage from control in AChE content in rats treated with LC recorded by LC group (-29.4%).

As showed in Table (1), records the Prophylactic effects of FC, Coq10 and their combination on brain (BDNF) in rats treated with LC. Lithium caused significant ($P>0.05$) decrease of BDNF (28.38). On another side FC, Coq10 and their combination showed amelioration effect for oxidative stress markers by increasing BDNF level in comparing with LC group Moreover, Fig. (1) showed % changes from control of FC, Coq10 and their combination on (BDNF) in rats treated with LC, we found FE group recorded 16.6%, followed by CoQ10 group 6.3%, then FE + CoQ10 + LC group (-6.3%), FE + LC group (-7.2%), CoQ10 + LC group (-18.2%), finally LC group (-33.9%).

Table 2: Prophylactic effects of FC, Coq10 and their combination on brain oxidative stress markers (GSH, GSSG and MDA) in rats treated with LC

Groups	Parameters		
	GSH	**GSSG**	**MDA**
Control	5.106 ± 0.32	0.428 ± 0.013	22.41 ± 1.232
FE	5.633 ± 0.28	0.404 ± 0.021	17.17 ± 1.647[a]
CoQ10	5.559 ± 0.361	0.410 ± 0.016	21.15 ± 1.410
LC	2.971 ± 0.303[a]	0.961 ± 0.036[a]	42.25 ± 2.894[a]
FE + LC	3.656 ± 0.353[ab]	0.665 ± 0.035[ab]	29.88 ± 1.582[ab]
CoQ10 + LC	4.187 ± 0.366[ab]	0.700 ± 0.039[ab]	33.80 ± 1.790[ab]
FE + CoQ10 + LC	4.649 ± 0.244[b]	0.612 ± 0.028[ab]	27.93 ± 1.108[ab]

Data are expressed as Mean ± S.E.M for 6 rats /group.
a significant difference from control group at the same column with one way ANOVA at P < 0.05.
b significant difference from L at the same column with one way ANOVA at P < 0.05.

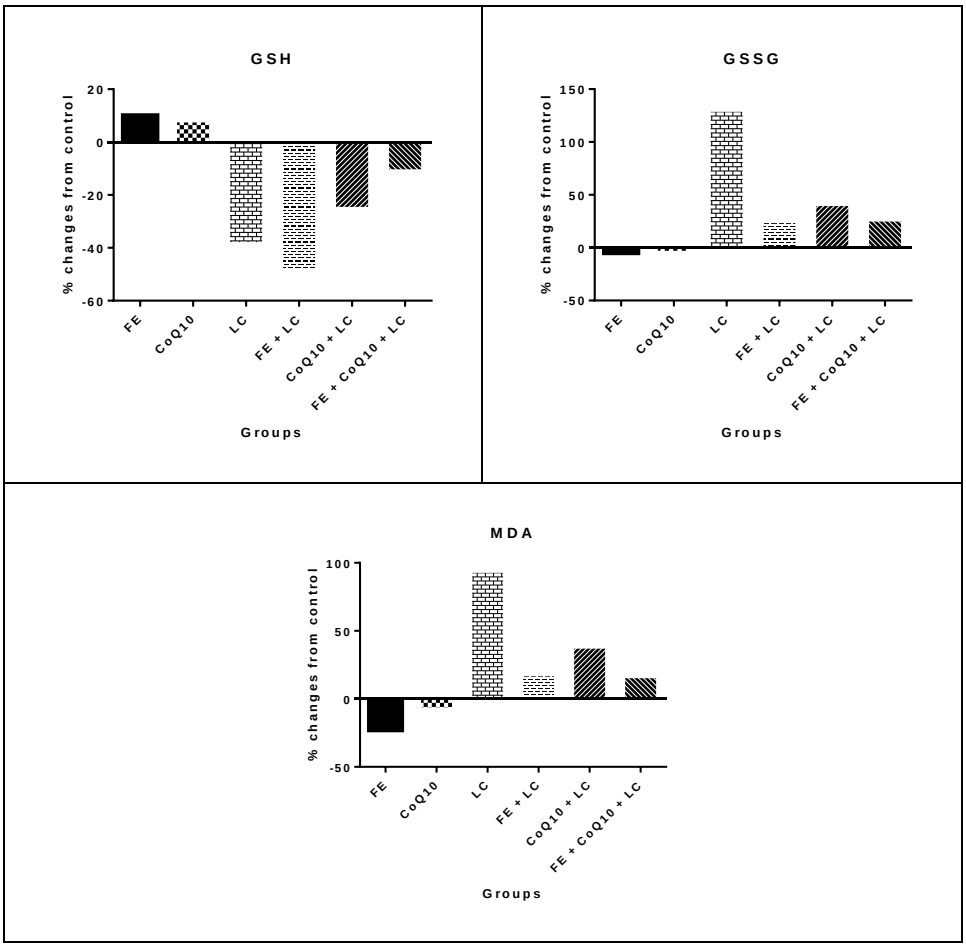


Figure 2: % changes from control of FC, Coq10 and their combination on brain oxidative stress markers (GSH, GSSG and MDA) in rats treated with LC.

The obtained data showed that there was no significant difference in GSH and GSSG between the control group and the FE, CoQ10 groups. Serum GSH values increased at the end of the experiment in the groups treated with (FC, Coq10) FE and CoQ10 (5.633 and 5.559) as compared to the LC group (2.971), Moreover, Fig. (2) showed % changes from control of FC, Coq10 and their combination on (GSH) in rats treated with LC, we found FE group recorded 10.4%, followed by CoQ10 group 8.8%, then FE + CoQ10 + LC group (-9.0%), CoQ10 + LC group (-18.0%), FE + LC group (-28.4%), finally LC group (-41.8%).

Moreover, we found serum GSSG values decreased at the end of the experiment in the groups treated with (FC, Coq10) FE and CoQ10 (0.404 and 0.410) as compared to the LC group (0.961), the percentage change (Fig. 2) of group (LC) as comparing with control group reached to 128.6% while this percentage decreased to -4.8% and -2.4% of groups FE and CoQ10, respectively.

From the results observed in above we found that group intoxicated with LC had a significant increase in MDA levels (42.25) when compared with a control group followed by group treated (CoQ10 + LC) recorded (33.80) then group (FE + LC) recorded (29.88), in another side group (FE) had the lowest value of MDA (17.17) there is a significant difference ($P < 0.05$) when compared with control group, In addition, Fig. (2) showed % changes from control of FC, Coq10 and their combination on (MDA) in rats treated with LC, we found LC group recorded (88.4%), followed by CoQ10 + LC group (50.9%), then FE + LC group (33.0%), FE + CoQ10 + LC group (24.6%), CoQ10 group (-5.8%), finally FE group (-23.7%).

Table 3: Prophylactic effects of FC, Coq10 and their combination on brain MPO and PGE2 in rats treated with LC

Groups	Parameters	
	MPO	**PGE2**
Control	9.14 ± 0.410	12.72 ± 0.63
FE	7.42 ± 0.593[a]	10.13 ± 0.88
CoQ10	8.63 ± 0.489	11.82 ± 0.70
LC	16.41 ± 0.99[a]	25.73 ± 1.74[a]
FE + LC	11.36 ± 0.47[ab]	16.34 ± 0.94[ab]
CoQ10 + LC	12.72 ± 0.68[ab]	18.41 ± 0.89[ab]
FE + CoQ10 + LC	10.91 ± 0.36[b]	15.28 ± 0.62[ab]

Data are expressed as Mean ± S.E.M for 6 rats /group.
a significant difference from control group at the same column with one way ANOVA at $P < 0.05$.
b significant difference from L at the same column with one way ANOVA at $P < 0.05$.

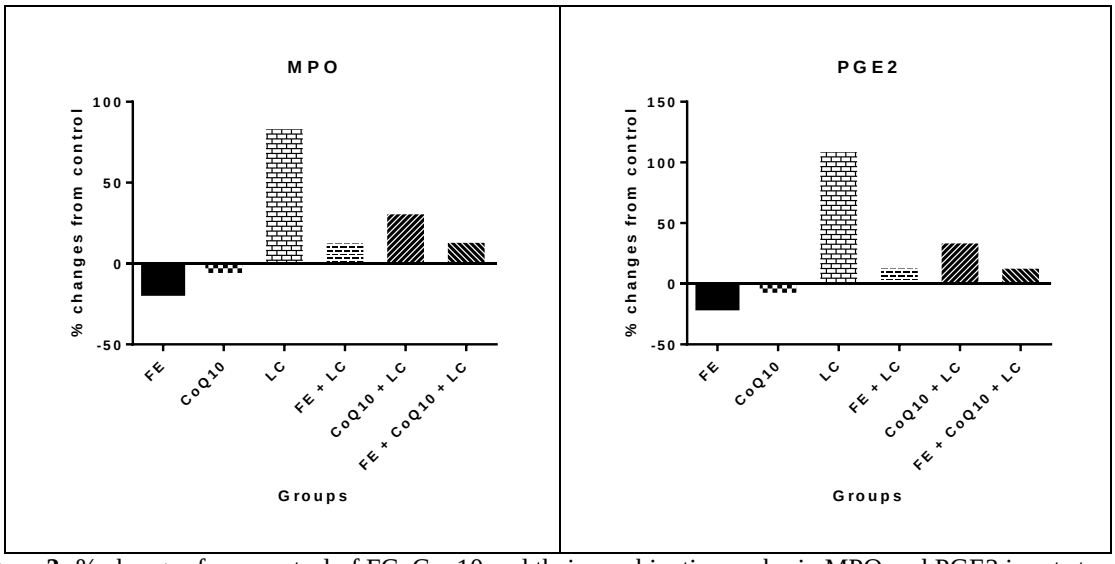


Figure 3: % changes from control of FC, Coq10 and their combination on brain MPO and PGE2 in rats treated with LC.

As showed in Table (3), records the Prophylactic effects of FC, Coq10 and their combination on brain (MPO and PGE2) in rats treated with LC. Lithium caused significant ($P>0.05$) increase of MPO and PGE2 to 16.41 and 25.73, respectively. On the other hand FC, Coq10 and their combination showed amelioration effect for oxidative stress markers (MPO and PGE2) by decreasing MPO and PGE2 level in comparing with LC group.

As illustrated in Fig. (3) changes from control of FC, Coq10 and their combination on (MPO) in rats treated with LC, we found LC group recorded 79.4%, followed by CoQ10 + LC group 38.9%, then FE + LC group (23.6%), FE + CoQ10 + LC group (19.3%), CoQ10 group (-5.6%), finally FE group (-18.8%). Similarly the change percentage in PGE2 level in FC, Coq10 and their combination from control LC group recorded 102.4%, followed by CoQ10 + LC group 44.9%, then FE + LC group (28.3%), FE + CoQ10 + LC group (19.7%), CoQ10 group (-7.1%), finally FE group (-20.5%).

Table 4: Prophylactic effects of FC, Coq10 and their combination on brain inflammatory mediators (IL-1 β and IL-6) in rats treated with LC

Groups	Parameters	
	IL-1 β	**IL-6**
Control	23.55 ± 0.276	14.62 ± 0.627
FE	22.07 ± 0.944[a]	13.44 ± 1.215
CoQ10	21.34 ± 0.986[a]	15.25 ± 0.583
LC	34.89 ± 1.823[a]	23.97 ± 0.994[a]
FE + LC	24.9 ± 0.920[b]	16.07 ± 0.788[b]
CoQ10 + LC	28.90 ± 1.268[ab]	20.60 ± 1.490[ab]
FE + CoQ10 + LC	22.90 ± 0.773[b]	16.70 ± 0.776[b]

Data are expressed as Mean ± S.E.M for 6 rats /group.
a significant difference from control group at the same column with one way ANOVA at $P < 0.05$.
b significant difference from L at the same column with one way ANOVA at $P < 0.05$.

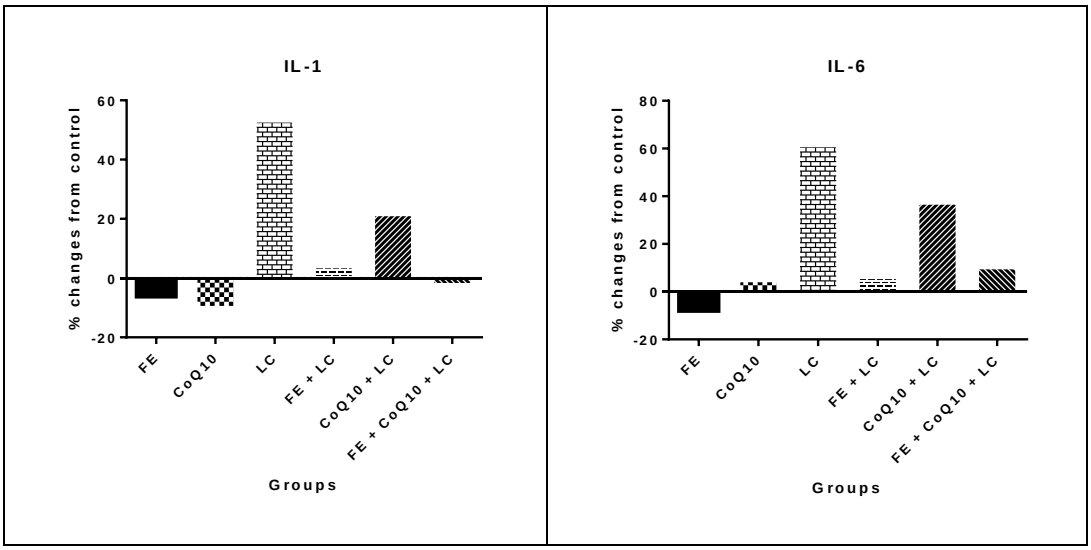


Figure 4: % changes from control of FC, Coq10 and their combination on brain inflammatory mediators (IL-1 and IL-6) in treated rats with LC.

A recent results states that increased IL-1β levels in LC group (34.89) when accompanied with control group (23.55), we found from results observed in Table (4) there is no big difference between groups (FE, CoQ10, and FE + CoQ10 + LC) as (22.07, 21.34 , and 22.90), respectively, in IL-1β levels when compared with the control group (23.55), Moreover, Fig. (4) showed % changes from control of FC, Coq10 and their mixture on (IL-1) in treated rats with LC, we found LC group recorded 48.1%, followed by CoQ10 + LC group 23.0%, then FE + LC group (6.0 %), FE + CoQ10 + LC group (-2.6 %), FE group (-6.4%), finally CoQ10 group (-9.4%). Otherwise, Table (4) showed an increase in IL-6 level in groups LC and CoQ10 + LC as following 23.97 and 20.6 when compared with the control group (14.62). Moreover, there is no big difference between groups FE and CoQ10 in IL-6 content (13.44 and 15.25) when compared with the control group (14.62). In addition, Fig. (4) showed % changes from control of FC, Coq10 and their mixture on (IL-6) in treated rats with LC, we found LC group recorded (63.7%), followed by CoQ10 + LC group (41.1%), then FE + CoQ10 + LC group (14.4%), FE + LC group (9.6%), CoQ10 group (4.1%), finally FE group (-8.2%).

IV. Discussion

Serotonin is known to be major endogenous anticonvulsants (Hattori et al., 1985 and Pasini et al., 1992). The study of (Tork, 1990) illustrated that serotonin neurons originate, in human lower brain stem raphe nuclei, including the dorsal and median, and project to all regions of the brain. Also, (Staley et al., 1998) described serotonin role in organizing such biological processes as mood and appetite in humans. Therefore, sedative and hypnotic action of LC may be due to the increased concentration of norepinephrine brain (Gupta et al., 1984).

Also, the protective effect of FC by decreasing of testes oxidative stress markers as protective agent for LC may be due to the phytochemical constituent (phenol, flavonoid, coumarins and tannins) that act as antioxidant by reducing the production of reactive oxygen species (Perez-Garcia et al., 2000; Algohary et al., 2016). According to (Mada et al., 2014) the flavanoids probability did so by reducing the accumulation of LC due to tannins which act as chelating agent.

Table (2): showed the effects of FC, Coq10 and their combination on brain oxidative stress markers (GSH, GSSG and MDA) in rats treated with LC. The present study provided evidence that LC increases brain oxidative stress, i.e increases the MDA and GSSG but decreases the reduced glutathione (GSH) in rat brain tissues, indicating the increase in GSH content. The glutathione- dependent antioxidant system plays a fundamental role in cellular defense against reactive free radicals and other oxidant species (Sen and Hänninen, 1994; Sen, 1997; Gul et al., 2000). On the contrary, we found that a significant difference between LC group and control group in GSH value due to the toxicity effect of LC in rat serum. The toxicity of lithium carbonate was evaluated by many investigations; Lithium inhibited glycogen synthase kinase-3, which is involved in a vast field of signal transduction paths. This effect occurs at high concentrations of lithium and may be more relevant for its toxic effect (Shaldubina et al., 2001),

the percentage change (Fig. 2) of group (LC) as comparing with control group may be due to (FC) have active ingredients that are capable of free radical scavenging in living system (Nikolova et al., 2011; Kumar et al., 2012). Phenolic compound are promising bioactive secondary metabolites playing an important role in detoxification of free radicals (Shanmugasundaram and Venkataraman 2006; Chon et al., 2008).

The toxic effects of Li on brain suggest that Li might affect the respiratory system via the systemic circulation the increase of MDA level of the Li-administered rats suggests that oxidative stress like lipid peroxidation might have formed. Biochemically, MDA, a marker of lipid peroxidation in the brain tissue, was found to be statistically higher in LC group rats than the control group (p 0.05). Previous researches reported increased lipid peroxidation in brain cortex due to lithium. (Sawas and Gilbert 1985), (Oktem et al., 2005), many researches have been conducted to detect the causality of free radicals in the pathogenesis of toxic substances. (Ozyurt et al., 2004) and (Gurel et al., 2004).

As showed in Table (3), records the Prophylactic effects of FC, Coq10 and their combination on brain (MPO and PGE2) in rats treated with LC. The protective effect of FC by decreasing of testes oxidative stress markers as protective agent for LC may be due to the phytochemical constituent (phenol, flavonoid, coumarins and tannins) that act as antioxidant by reducing production of reactive oxygen species (Perez-Garcia et al., 2000; Algohary et al., 2016).

IL-1 is a versatile cytokine, which has unique physiological roles, including cytokine secretion in autoimmune diseases, vascular permeability, and induction of fever in sepsis (Dinarello 1996). Many researches illustrated that increased IL-1 excretion boosts the genes expression which encode proteins involved in metastasis [i.e., matrix metalloproteinases (MMPs)], and secretion of growth and angiogenic factors, which inclusive the vascular endothelial growth factor (VEGF), IL-8, IL-6, TNF-α and transforming growth factor-β (Konishi et al., 2005 and Barillé et al., 1997). Furthermore, IL-1 receptor antagonist (IL-1Ra) is an organ of the IL-1 family, having parity with IL-1α and IL-1β (Apte and Voronov 2002).

According to (Lewis et al., 2006) IL-1 is a many-sided cytokine, plays a major role not only in physiological processes, but also in pathological processes, such as those involved with autoimmune diseases, sepsis, and malignancies. The IL-1 family made up of pro-inflammatory and immunoregulatory cytokines, including IL-1α, IL-1β and IL-1Ra (Voronov et al., 2007). IL-1α and IL-1-β act as stimulants, while IL-1Ra has anti stimulants effects. Although IL-1α and IL-1-β are encoded on different genes, they bind to the identical receptor with similar functions (Dinarello 1991). By contrast, IL-1β is first processed by IL-1β converting enzyme, and later manifested as a mature form is subsequently secreted. Increase in IL-1β concentration in case of inflammation or infection, instead of IL-1α, suggests that IL-1β Practice systemic effects (Dinarello 1991).

Otherwise, table (4) showed an increase in IL-6 level in groups LC and CoQ10 + LC when compared with the control group. Moreover, there is no big difference between groups FE and CoQ10 in IL-6 content when compared with the control group. In addition, Fig. (4) showed % changes from control of FC, Coq10 and their mixture on (IL-6) in treated rats with LC, Proinflammatory cytokines interleukin 1 beta (IL-1β), interleukin 6 (IL-6) and tumor necrosis factor alpha (TNF-α) Practice various biological functions. Apart from regulating inflammatory response, these cytokines play important role in the development of cancer. IL-1β acts as a potent promoter of cancerogenesis by enhancing the action of chemical cancerogens which results in proliferation of mutated cells and further accumulation of genetic damage (Dinarello 1996).

V. Conclusion

On the whole, Obtained data concluded that LC acts like a bipolar treatment but increase neuro toxicity through increase oxidative stress markers and inflammatory cytokines. Alternatively, FC, CoQ10 and their combination ameliorate negative impacts of LC and can normalize bipolar symptoms.

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IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) is UGC approved Journal with Sl. No. 5012, Journal no. 49063.

Devaraja S" Adaptogenic neuronal activity of ficus carica and ubiquinone on neuron-toxicity and oxidative stress in lithium carbonate treated rats" IOSR Journal of Pharmacy and Biological Sciences (IOSR-JPBS) 14.1 (2019): 73-82.