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Protective role of turmeric extract (*Curcuma longa*) in the lipid profile and activity of antioxidant in the male rats treated by lithium carbonate

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Abstract: The antioxidant effect of turmeric (*Curcuma longa*) extract against side effects induced by lithium carbonate (Li2CO3) were studied. The experiment was carried out on fifty male rats distributed randomly into 5 groups of 10 animals in eachgroup.The (1) group was kept as a normal control was received normal saline, rats of group (2) and (3) were given only lithium carbonate only in a dose 4 and 8 mg/kg for induction of oxidative state on rats, While other groups (4) was received lithium carbonate at dose 4 mg/kg with turmeric extract at dose 1 g for 1 kg of diet and groups (5) was received lithium carbonate at dose 8 mg/kg with turmeric extract at dose 1 g for 1 kg of diet. Results showed that oral administration of turmeric extract in rats with oxidative state by Li2CO3 decrease the lipid profile parameters and increase antioxidant enzymes. Conclusively: treatment by turmeric extract was produce a protective effect against oxidative stress by Li2CO3 in the male rats.
Keywords: lithium, lipid profile, lipid peroxidation, glutathione peroxidase, superoxide dismutase, male rat.

Introduction

Lithium is used in medicine more than 50 years [1] especially in manic depression. However, lithium is applied in many fields as lithium therapy[2,3,4,] neurodegenerative disease [5,6]. The usefulness of lithium in cure of bipolar disorder was reported in many researches [7]. On other side, many studies were recorded adverse effects of lithium in the human [8,9,10]. The ROS are substances synthesized in the body during the normal metabolic processes as a series of incomplete reduction of oxygen molecule [11,12]. The living organisms are protect themselves from oxidative stress by producing antioxidants represent molecules having the capability to scavenge ROS[13,14].

Lithium have a wide medical applications and major in the balance between anti and pro-oxidative processes.In addition, lithium also effect on lipid metabolism during changes thyroid hormones levels [15]. The precise mechanism to explain how lithium change the lipid metabolism is unknown[16].

However, little data about the changes in lipoprotein metabolism during lithium treatment. Some authors demonstrated the relationship between the lithium side effects and lipids metabolism. These studies were suggested the changes in plasma lipid and lipoprotein levels following lithium treatment. This is very essential in psychiatric patients when taken lithium for long period[17].

Materials and methods

Lithium carbonate (Li2CO3) was purchased from the Norginecompany, U.K.

Turmeric rhizomes were purchased from the local market in AL-Najaf city.

Preparation of phenolic extract of turmeric (curcuminoids): The rhizomes were crushed to powder by using a blender, take a bout 100g of powdered were added to 500ml of 80% ethanol and put the mixture in soxhelt system during 24h. After that, resulting extracts were filtered using filter paper and concentrated to dryness in rotary evaporator in the room temperature.

Then, the recipient was transferred to a separating funnel, and 2 N (HCl) were added gradually to get pH 2, then, washed with 10 ml chloroform three times. The solution was separated into two levels, the down level contain the phenols (curcuminoids) were residue, weighted and kept in a refrigerated until using it [18].

Determination of lipid profile activity

Total cholesterol kit for quantitative determination of total cholesterol in serum was supplied by Biolabo SA, France[19].

Serum HDL-Cholesterol level was measured by HDL-Cholesterol phosphotungstic acid (PTA) precipitant kit (Biolabo, France)[19].

Very low density lipoprotein (VLDL) were measured by using the following formula: VLDL = TG (mg/dl) / 5[19].

Low density lipoprotein (LDL) were measured by using the next formula: LDL=TC(mmol/l)-VLDL(mmol/l)-HDL(mmol/l)[19].

Triglycerides Kit was supplied by Biolabo, France, for measuring triglycerides in human serum [20].

Determination of antioxidant enzymes

Measurment of SOD activity by ELISA Kit (Elabscience, U.S.A.) (www.elabscience.com).

The quantitativedetermination of GPX concentration in serum through the enzyme linked immunosorbant assay using ELISA kit (Elabscience, U.S.A.) (www.elabscience.com).

Measurment of MDA activity by ELISA Kit (Elabscience, U.S.A.) is an enzyme immunoassay (www.elabscience.com).

Experimental Design:

Fifty male albino rats strain (*Rattusn orvegicus*) weighting (225-250g) obtained from the animal house in the science faculty/Kufa university. The rats kept under observation for one week before starting the experiment for acclimatization. fed on standard diet and water *ad libitum* .Then animals were divided into five groups of six rats in each. The first group was fed on the basal diet, normal saline and served as control. The second and third groups were received lithium carbonate at doses 4, 8 mg/kg respectively. The fourth and fifth groups were administration lithium carbonate at dose 4, 8 mg/kg plus turmeric extract (curcuminoids) at dose 1 g/1 kg respectively for 6, 8 weeks.Half number of rats from each groupafter 6 weeks of experiment were anaesthetized by Ketamine and xylazine and blood samples have collected by heart puncture and put into serum tubes in the room temperature for several minutes and were centrifuged for 20 minutes at 3000 rpm. At the end of experiment (8 weeks) the remainder of rats also anaesthetized by the same method and the blood samples were saved.

Statistical Analysis: Data were expressed as mean±S.E. and Statistical Analysis was carried using computerized SPSS program version (21) with one way ANOVA[21].

Results and Discussion:

The results in table (1) and (2) show significant increase in the total cholesterol, triglycerides, low density lipoprotein and very low density lipoprotein in the serum of rats administration of lithium carbonate for six, eight weeks. The present results demonstrated that lithium, even at therapeutic doses, disturbs lipid metabolism. This disturbance may be started by the changes in the activity of lipoprotein lipase, a initial enzyme that plays an important role in the metabolism, transport and tissue uptake of lipid fractions. Lithium is shown to reduce the activity of this enzyme. The inhibitory effect of lithium was potentiated in the presence of citrate. It had already been recorded that citrate makes lithium very soluble and a lot of works were undertaken to make citrate salt of lithium for therapeutic purposes [22]. The precise mechanism by which lithium inhibits lipoprotein lipase activity was not known closely, however the activity of this enzyme depends on the presence of free-SH groups [23]. It is possible that lithium by interacting with some essential-SH groups in the active site of the enzyme reduces enzyme activity.

In addition, in the present study used turmeric extract (curcuminoids). The main component of curcuminoids was curcumin .antioxidant activity of curcumin has been reported as early as 1975. It acts as a scavenger of oxygen free radicals[24]. *In vitro*, curcumin can significantly inhibit the generation of reactive oxygen species (ROS) such as superoxide anions, H_2O_2, and nitrite radical generation by activated macrophages, which play an important role in inflammation[25]. curcumin reduces serum and liver cholesterol levels in mice[26] and also reported to have anti-inflammatory activity in standard animal models[27]. It has been reported by Ruby[28] studying the antitumor and antioxidant activity of natural curcuminoids that curcumin inhibits the generationof superoxide radicals. curcumin also reduced lipid peroxidation in rat liver microsomes, erythrocyte membranes, and brain homogenates[29,30]. Because ROS had been implicated in the development of potential to control these diseases though it was antioxidant activity. Several studies have reported the antioxidant property of curcumin, increment endogenous antioxidant levels[31]. curcumin also inhibits the induction of nitric oxide synthase in activated macrophages and down regulates nitric oxide formation[32,33].

The results in the table (3) and (4) reported significant decrease ($p<0.05$) in the levels of SOD and GPX and significant increase ($p<0.05$) in the level of MDA. In the group of rats were demonstrated lithium carbonate only for the 6, 8 weeks. Several studies were recorded lithium toxicity can be connected with oxidative stress [34,35,36,37] but contradicting outcomes were also reported[38,39]. Furthermore, oxidative stress was also found to be involved into the pathophysiology of bipolar disorder[40]. As long term lithium therapy was used in the cure of this disease, the question of the influence of lithium on oxidative processes was an issue of great importance. The organisms developed a complex system of defense against oxidative stress which includes numerous substances, among other things antioxidant enzymes, namely superoxide dismutase, glutathione peroxidase and catalase [41,42].

Lithium given for a longer period (2 months) caused a significant decrease in SOD and GPX in rats. Naziroglu[43] found decreased SOD and GPX in healthy subjects undergoing lithium treatment. These outcomes seem to confirm our assumption regarding possible adjuvant application of any antioxidant in lithium treatment.

Intraperitoneal lithium treatment for a period of 7 days changed neither SOD nor GPX in rat livers[44]. Lithium carbonate provided to rats in drinking water for a period of 4 weeks markedly influenced neither GPX nor SOD in liver. Lipid peroxidation (MDA) was also unaffected[45]. In other study one month administration in diet resulted in the decrease of hepatic lipid peroxidation in rats under different dietary regimens[46]. Chinese scientists lithium and Long reported that lithium exerted the divergent effect on lipid peroxidation in rat livers. Lower doses resulted in inhibition, whereas the higher concentrations showed a stimulating influence[47]. An increased GPX activity in the liver of diabetic rats was observed, whereas SOD remained unchanged as a consequence of lithium treatment [48]. However, it has already been mentioned that differences of the lithium's action in physiologic and pathologic states in rats were observed. Concerning human beings, it has also been reported that the lithium effect on cognitive functions differed in healthy subjects from that found in psychiatric patients [49].

In addition, the results show Dietary turmeric lowered lipid peroxidation by enhancing the activities of antioxidant enzymes its conform with previous studies[50].

It exerted beneficial effect in preventing oxidative stress in rats [51]. Dietary antioxidants have preventative effects on oxidative stress. The antioxidant mechanism of turmeric was attributed to its major component in curcuminoid compoundes called curcumin. curcumin was conjugated structure which includes two methoxylated phenols and an enol form of β-diketone. The structure showed a typical radical trapping ability as a chain breaking antioxidant [52]. Curcumin exhibit a differential antioxidant activity in several *in vitro* and *in vivo* models, for example, preventing lipid peroxidation in a variety of cells such as erythrocytes and rat liver microsomes, where peroxidation is induced by Fenton's reagent, as well as for metals and hydrogen peroxide (H_2O_2). Furthermore, it has been reported that curcumin is a bi-functional antioxidant [53], because of its ability to react directly with reactive species and to induce an up-regulation of various cytoprotective and antioxidant proteins. Curcumin is able to scavenge superoxide anion (O2-.)[54,55], hydroxyl radicals (.OH)[56], singlet oxygen[57], nitric oxide[58], peroxynitriteand peroxyl radicals (ROO.)[59].

Together, these mechanisms might explain, at least in part, some of the cytoprotective effects of this compound. Features as the presence of phenolic groups in the structure of curcumin explains its ability to react with reactive oxygen species (ROS) and reactive nitrogen species (RNS) and might probably be one of the mechanisms through which curcumin treatment protects erythrocytes from oxidative damage.

In conclusion

Oral administration of turmeric extract (*curcumalonga*) to toxicity male rats for 6, 8 weeks decrease the lipid profile parameters also increase antioxidant enzyme levels in serum. Therefore, this study recommended that intake of turmeric in food may be useful for patients who suffer from manic depression to reduce the side effects of lithium when taken for long period.

Table (1) Effect of the interference between the extracts and dose in the lipid profile levels in the rats treated with lithium carbonate for six weeks.

Treatment	Dose	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	VLDL (mg/dl)	LDL (mg/dl)
Li2CO3	4 mg/kg	63.67±2.88	53.67±16.86	26.33±5.03	10.73±3.37	26.60±8.87
	8 mg/kg	81.33±1.15	60.33±19.55	41.33±2.08	12.07±3.91	27.93±2.91
Li2CO3& C	4 mg/kg	59.33±1.15	34.00±5.29	34.33±4.50	6.80±1.05	15.53±0.81
	8 mg/kg	63.33±4.16	36.33±3.21	45.00±6.55	7.27±0.64	11.07±7.10
Control		49.33±15.04	25.33±12.85	37.00±8.54	6.67±1.52	7.00±3.00
L.S.D. 0.05		11.592	13.454	8.565	2.694	6.581

Number of animals = 5 for each group Each value represents mean ± S.E.
Li2CO3 : Lithium carbonate C : Turmeric extract (Curcuminoids)

Table (2) Effect of the interference between the extracts and dose in the lipid profile levels in the rats treated with lithium carbonate for eight weeks.

Treatment	Dose	TC (mg/dl)	TG (mg/dl)	HDL (mg/dl)	VLDL (mg/dl)	LDL (mg/dl)
Li2CO3	4 mg/kg	84.00±3.60	62.67±2.51	23.67±3.21	12.53±0.50	47.80±6.23
	8 mg/kg	102.00±7.21	71.67±6.65	19.33±1.15	14.33±1.33	68.33±6.99
Li2CO3& C	4 mg/kg	51.67±2.88	36.00±1.73	41.67±2.88	7.20±0.34	2.80±0.34
	8 mg/kg	57.67±3.06	46.67±4.04	46.33±3.21	9.33±0.81	2.00±1.05
Control		46.67±15.27	25.33±11.01	39.33±9.01	8.00±2.00	9.00±3.60
L.S.D. 0.05		11.592	13.454	8.565	2.694	6.581

Number of animals = 5 for each group Each value represents mean ± S.E.
Li2CO3 : Lithium carbonate C : Turmeric extract (Curcuminoids).

Table (3) Effect of the interference between the extracts and dose in the antioxidant levels in the rats treated with lithium carbonate for six weeks.

Treatment	Dose	MDA (ng/ml)	SOD (ng/ml)	GPX (pg/ml)
Li2CO3	4 mg/kg	27.33±1.36	0.35±0.03	91.99±28.36
	8 mg/kg	33.11±8.95	0.24±0.05	53.57±15.39
Li2CO3& C	4 mg/kg	23.94±4.39	0.16±0.06	44.00±15.85
	8 mg/kg	20.92±2.68	0.14±0.01	47.12±17.26
Control		24.73±2.31	0.19±0.04	82.77±27.26
L.S.D. 0.05		14.128	0.185	36.340

Number of animals = 5 for each group Each value represents mean ± S.E.
Li2CO3 : Lithium carbonate C : Turmeric extract (Curcuminoids)

Table (4) Effect of the interference between the extracts and dose in the antioxidant levels in the rats treated with lithium carbonate for eight weeks.

Treatment	Dose	MDA (ng/ml)	SOD (ng/ml)	GPX (pg/ml)
Li2CO3	4 mg/kg	32.29±14.20	0.10±0.06	64.47±25.63
	8 mg/kg	31.47±12.31	0.11±0.02	56.23±45.20
Li2CO3& C	4 mg/kg	32.44±15.20	0.19±0.02	75.63±20.69
	8 mg/kg	32.69±12.10	0.18±0.03	55.28±31.52
Control		23.68±10.10	0.20±0.04	78.56±19.19
L.S.D. 0.05		14.128	0.185	36.340

Number of animals = 5 for each group Each value represents mean ± S.E.
Li2CO3 : Lithium carbonate C : Turmeric extract (Curcuminoids)

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