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Effect of turmeric extract (*Curcuma longa*) on physiological parameters and neurotransmitters in rats treated by lithium carbonate

Afyaa Sabah Nasir*, Haider Salih Jaffat

Science Faculty, University of Kufa, Najaf, Iraq

Abstract: The present study suggested the therapeutic effect of turmeric (*Curcuma longa*) extract against oxidative stress induced by lithium carbonate (Li2CO3) are studied. The experiment is designed on fifty male rats spread randomly into 5 groups of 10 animals in each group. Thefirstgroup is received normal saline as normal control, the second and third groups are given lithium carbonate only at dose 4 and 8 mg/kg for induction of oxidative state on rats, While the fourth group is received lithium carbonate at dose 4 mg/kg with turmeric extract (curcuminoids) at dose 1 g for 1 kg of diet and the fifth group is received lithium carbonate at dose 8 mg/kg with turmeric extract (curcuminoids) at dose 1 g for 1 kg of diet. Results showed that oral administration of turmeric extract in rats with oxidative state by Li2CO3 increase the red blood corpuscles (RBCS), haemoglobin concentration (Hb), packed cell volume (PCV) and decrease the white blood cells (WBCS), erythrocyte sedimentation rate (ESR).At the same time, the results appear increase dopamine level and decrease serotonin level in groups administrated lithium carbonate and curcuminoids. In conclusion: turmeric has beneficial effect against side effects induced by Li2CO3 in rats.
Keywords: lithium carbonate, oxidative stress, blood parameters, liver enzymes.

Introduction

In 1811 lithium is discovered by Arfwedson[1]. Lithium carbonate (Li2CO3) is one salts of lithium mainly used to treatment of manic depression[2,3]. The therapeutic uses of lithium in depression, schizoaffective disorder, aggression, impulse control disorder, eating disorders, attention deficit disorder and in certain subsets of alcoholism. Lithium from alkali group of metals, having atomic no.3 and atomic weight of 6.93. It is water soluble, not bound with protein and dispersed in all body fluids include plasma and extracellular fluids[4].Lithium was readily absorbed after oral administration and its peak level was reached in 2-4 hrs. About 95% of absorbed lithium carbonate was excreted in urine; about 1% in feces and 4-5 % in sweat[5]. Lithium binds poorly to high and low molecular weight plasma proteins but binds strongly to very low molecular weight ligands. As it moves slowly from extracellular compartment to intracellular space, it may require 6-8 days to reach steady blood concentration and desired therapeutic responses[6].

Also, lithium has used in many medical disorders, specially cluster headache and dermatological disorders (seborrheic dermatitis, eczematoid dermatitis, and genital herpes)[7]. Initially, lithium was used to treat Urinary calculi and gout with little success, till Cade [8]reported its antimanic effect.

Distribution of lithium in the human organs is almost uniform; it was concentrated in tissues like brain, kidney, thyroid, bone, liver, and muscle cells against concentration gradient. Lithium becomes widely

distributed in the central nervous system and interacts with a number of neurotransmitters, decreasing norepinephrine release and increasing serotonin synthesis [9].

Curcuma longa (turmeric) is widely used widely as a spice and coloring agent in many foods. Turmeric component has been related with many useful properties to human health as defense against inflammatory, apoptosis and oxidative stress[10]. Curcuminoids are the chief active component of turmeric. There properties a yellow phenolic pigment consequent from the turmeric rhizome which have a wide-ranging of biological and pharmacological activities. Curcuminoids have been demanded to be a potential anti-inflammatory, antineoplastic and antimutagenic agent [11].In addition, have antioxidant effect by inhibiting producing of ROS both *in vitro* and *in vivo*[12].

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 [13].

The haematological parameters were performed on EDTA blood using Ruby (Abbott., U.S.A), Ruby is haematology analyser to perform red blood cell (RBC), white blood cell (WBC), haemoglobin (HB), ESR and packed cell volume (PCV) on EDTA [14].

Determination of neurotransmitters

This laboratory test was determine by ELISA kit (Elabscience,U.S.A.) (www.elabscience.com).

The levels of serotonin in serum were evaluate byELISA kit (Elabscience, U.S.A.) (www.elabscience.com).

Experimental Design:

Fifty male albino rats strain (*Rattus norvegicus*) 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 group after 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[15].

Results and Discussion:

The results of the current study show significant increment ($p<0.05$) in the Red blood corpuscles, Haemoglobin concentration, Packed cell volume and significant decrement ($p<0.05$) of leucocytes count,

Erythrocyte sedimentation rate after administration of lithium carbonate for eight weeks in comparison with control group and this results agreement with [16] while no significant ($p>0.05$) in blood parameters in animals administration of lithium carbonate for six weeks due to short period of administration is not sufficient to cause the significant changes.

So that lithium given for a period of two months did affect significantly in decrease red blood corpuscles, haemoglobin and haematocrit in rats, but a well marked increase in total leukocyte counts and erythrocyte sedimentation rate may be lithium administration can influence in the immune system [17].

Lithium toxicity lead to produce free radicals which act on oxidation of unsaturated lipids in the erythrocyte membranes lead to increase the fragility and rapid analysis. also lithium inhibit glutathione present in the red blood corpuscles responsible to remove the harmful free radicals from the hydrogen peroxide inside the red blood corpuscles cause to damage the membrane of the red blood corpuscles lead to break down simply [18].

In addition the reduction in erythrocyte production attributed with reduce haemoglobin level because lithium inhibit biosynthesis of heme molecule by inhibit Delta amino levulinic acid dehydrarase (d-ALAD) which play important role in the first steps of biosynthesis of heme molecule was a principle component of haemoglobin[19].

The decrease in the packed cell volume comes from the decrement the numbers of red blood corpuscles in away and decrease the haemoglobin concentration in another way [20]. the packed cell volume was directly proportional to the number of red blood corpuscles which reported by Campos and Luis [21] are refer to increase in packed cell volume due to increase of red blood corpuscles.

These results agreement with observations of[22,23,24] are demonstrated the erythrogram showed significant decrease in the values of RBC's count, haemoglobin concentration and packed cell volume in high dose cadmium exposed groups.

This study was reported that cadmium intoxication induced oxidative stress and altered the antioxidant system, that may result in oxidative damage by inhibition of erythrocyte Na - K ATP ase leading to loss of cell membrane integrity and functions, shortened life span of erythrocyte and occurrence of anemia [25,26].

Also, the present study show significant increase ($p<0.05$) in leucocytes counts and erythrocyte sedimentation rate because lithium cause inflammation in the joints of the laboratory animals were treated with lithium carbonate lead to increase the erythrocyte sedimentation rate as well as the inflammation occur in the smooth muscles, liver, lung and skin as a results increase production of the total leucocytes counts in the bone marrow, these results accepted with Hus and Guo[27].

Assessment of the effect of different antioxidants in the present study on the haemogram. curcuminoids (the phenolic extract of turmeric). Treatment with curcuminoids are effective in reducing oxidative damage induced by lithium carbonate. curcuminoidsare capable of inhibiting production of ROS which caused haemolysis, through its high antioxidant activity [28,29,30].

Curcumin is a major component in curcuminoids play important role as antioxidants an effective on cadimum intoxication treatment. These results agreement with lalitha and selvam[31] are recorded the inhibitory effect of turmeric on cadimum induced lipidperoxidation in blood and suggested that, curcuminoids provided a protection against lipid peroxidation and haemolysis of red blood corpuscles induced by H2O2.

The antioxidant mechanism of curcuminoids are attributed with curcumin molecule has 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 [32]. 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 was induced by Fenton's reagent, as well as for metals and hydrogen peroxide (H2O2)[33]. Moreover, it has been reported that curcumin is a difunctional antioxidant[34], because of its capacity to react directly with reactive species and to induce an up-regulation of various cytoprotective and antioxidant proteins. Curcumin is capable to remove superoxide anion (O2-.)[35,36], hydroxyl radicals (.OH) , single oxygen (O.)[37,38], nitric oxide[39], peroxynitrite and peroxyl radicals (ROO.)[40].

All, these mechanisms has 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 capability 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 stress[41].

Lithium's therapeutic efficacy in bipolar disorder depends partly on its normalizing a cholinergic–dopaminergic neurotransmission imbalance, may be the imbalance involves signaling via Phospholipase-A2 rather than via other receptor coupled effector enzymes (e.g. adenylatecyclase, phospholipase C (PLC)[42]. Supporting this interpretation are observations in rats that lithium feeding recorded a significant decrease ($p<0.05$) in the dopamine level and a significant increase ($p<0.05$) in the serotonin level in the serum of rats after administration of lithium carbonate and chromium picolinate for six and eight weeks.reducesarecoline-initiated hydrolysis of phosphatidylinositol-4,5-bisphosphate by phospholipase C (PLC) in the brain, that lithium is a pro-convulsant with regard to arecoline and other cholinomimetics[43,44,45] and that it does not inhibit dopamine sensitive accumulation of cyclic AMP in the guinea pig brain[46].

Serotonin level have been reported to increase following oxidative stress in the rats[47,48,49]. An ample evidence indicate that dysfunction of serotoninergic neurotransmission in CNS is involved in the development of depression, anxiety and memory disorders[50,51]. Increased level of brain 5-HT enhances memory[52] whereas decreased level of brain 5-HT impairs cognitive performance [53]. Hence, it can be suggested that administration of lithium increases cognitive performance due to increase in 5-HT level in the animals.This enhancing effect of lithium on 5-HT largely support the previous data[54]. Lithium increases the 5-HT turnover rate[55] and the levels of 5-HT as well as its precursor tryptophan in the brain. However, under oxidative stress primary actions of repeated treatment with lithium salts on 5-HT may be presynaptical, which stimulates serotonin synthesis and 5-HT release in raphe neurons[56].

In the current study was recorded the useful effect of turmeric extract against oxidative stress induced by lithium carbonate and chromium picolinate by determine the levels of DA and 5-HT in the serum of rats after administration for six and eight weeks. Gasem*et al*[57] are reported the turmeric (curcuminoids) had a significantly ameliorating effect on the cadmium induced deficits in the body weight, anxiety behavior, learning capability (cognitive effect) and muscular activity. Biochemical analysis in forebrain tissue also revealed that curcuminoids significantly attenuated cadimum induced neurotransmitters (reportedly associated with locomotor and cognitive activities) and the cadmium induced oxidative stress related enzymes (associated with behavioral and cognitive deficits). Furthermore, the ineffectiveness of curcuminoids alone to cause any behavioral and biochemical deficits, clearly suggest that curcuminoids alone is non toxic and further supports for the ameliorating effect of curcuminoids on the behavioral and biochemical toxicity induced by cadmium [58,59]. The biochemical damage may be due to the fact that cadimum induces an oxidative stress that results in oxidative deterioration of biological macromolecules. curcuminoids reportedly has potent antioxidant activities [60], anti-inflammatory and chemoprotective properties [61]. It has been shown to have a neuroprotective effect in models of cerebral ischemia[62,63], ethanol induced brain damage [64] and reduced amyloid pathology in transgenic mice of Alzheimer's disease[65].

Generally metals can oxidize monoamines either directly or through oxygen free radicals production. Many studies have proposed that iron induces lipid peroxidation [66] and demonstrated in confirmation that Fe^{+2} behaves like oxidants (sodium percodate) and superoxide radicals. Where, this study showed an increase in serum iron and ferritin in iron overload group.

Dopamine biosynthesis may be also affected due to its exposure to mild oxidizing conditions leading to its partial oxidation. Dopamine quinones covalently modify cysteinyl residues in tryptophan hydroxylase (TPH; the rate limiting enzyme in serotonin), leading to loss of its catalytic activity [67].

However, serotonin and melatonin can inhibit reactive and mitochondria oxidation of thiols in addition to degradation of 2-deoxyribose. This may conclude the protective role of serotonin on iron mediated neuronal damage. disturbances in neurotransmitters levels like serotonin and dopamine and their oxidation metabolites may be associated with neurodegenerative diseases[68]. Thus, the obtained changes results from excess iron in brain may dispose the brain to developing neurodegenerative disorders such as Parkinson's and Alzheimer's diseases. Iron levels increase with the severity of neuropathological changes in Parkinson's disease (PD), presumably due to increased transport through the blood-brain barrier in late stages of parkinsonism[69].

Conclusion:

The present study proposed the use of turmeric could to alleviate adverse effects, in particular those related to oxidative stress that occurred in male rats after long period of oral administration of lithium carbonate.

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

Treatment	Dose	RBCs $x(10^6)$ cor/mm^3	Hb (mg/dl)	PCV (%)	WBC $x(10^3)$ cell/mm^3	ESR (mm/h)
Li2CO3	4 mg/kg	4.40±0.08	10.80±1.25	37.00±9.52	4.70±136.25	21.00±0.51
	8 mg/kg	4.36±0.12	10.50±1.36	34.20±8.32	8.78±142.20	32.40±0.42
Li2CO3 & C	4 mg/kg	5.74±0.52	11.78±1.22	38.60±12.57	5.10±142.20	10.40±1.30
	8 mg/kg	6.42±0.18	12.48±1.54	39.60±15.32	6.22±223.25	16.20±1.26
Control		5.00±0.51	12.80±1.21	38.40±5.36	6.40±123.89	4.00±2.02
L.S.D. 0.05		0.200	0.455	1.117	0.637	1.733

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 blood parameters in the rats treated with lithium carbonate for eight weeks.

Treatment	Dose	RBCs $x(10^6)$ cor/mm^3	Hb (mg/dl)	PCV (%)	WBC $x(10^3)$ cell/mm^3	ESR (mm/h)
Li2CO3	4 mg/kg	3.31±2.30	10.50±1.14	34.40±6.32	8.90±336.5	32.00±15.32
	8 mg/kg	3.17±1.20	9.60±1.25	33.40±2.56	11.53±5214.3	44.00±21.04
Li2CO3 & C	4 mg/kg	5.58±0.56	12.38±1.85	41.60±4.21	4.60±488.9	4.40±5.21
	8 mg/kg	6.05±0.33	11.80±1.69	36.40±3.33	5.38±587.5	8.20±6.32
Control		5.00±1.20	12.40±1.44	38.60±1.59	6.20±0.800.3	3.60±1.24
L.S.D. 0.05		0.200	0.455	1.117	0.637	1.733

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 levels of neurotransmitters in the rats treated with lithium carbonate for six weeks.

Treatment	Dose	DA (ng/ml)	5-HT (pg/ml)
Li2CO3	4 mg/kg	0.611±0.201	23.14±12.36
	8 mg/kg	0.564±0.152	31.82±10.85
Li2CO3 & C	4 mg/kg	0.899±0.110	16.92±8.52
	8 mg/kg	0.805±0.100	18.11±6.36
Control		1.492±0.032	17.06±5.20
L.S.D. 0.05		0.339	14.603

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 levels of neurotransmitters in the rats treated with lithium carbonate for eight weeks.

Treatment	Dose	DA (ng/ml)	5-HT (pg/ml)
Li2CO3	4 mg/kg	0.343±0.185	32.90±12.56
	8 mg/kg	0.272±0.057	50.07±14.32
Li2CO3 & C	4 mg/kg	0.831±0.175	22.85±14.85
	8 mg/kg	0.887±0.125	24.73±14.96
Control		1.459±0.541	16.39±5.62
L.S.D. 0.05		0.339	14.603

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

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