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The ameliorative effect of dietary supplementation of Curcumin on 1,2-dichloroethane (1,2DCE) -induced oxidative stress in rat organs

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ABSTRACT

Curcumin was investigated for a possible anti-oxidant influence against 1,2-dichloroethane (1,2DCE) induced oxidative stress in rats. Fifty male adult male albino rats were divided into five groups (10 rats each). G1 served as negative control fed basal diet, G2 (positive control) fed basal diet contain 1,2DCE for 4 weeks, G3 (Protective group) fed standard diet supplemented with curcumin as 1.5 g/kg/diet for 4 weeks , then 1, 2-dichloroethane was added to diet for further 4 weeks. G4 (Preventive group) fed standard diet with curcumin as 1.5 g/kg/diet for 4 weeks along with 1, 2-dichloroethane for 4 weeks. G5 (Curative group) fed standard diet + 1, 2-dichloroethane for 4 weeks after that, the diet supplemented with curcumin as 1.5 g/kg/diet for 4 weeks. Biochemical parameters including RNA, DNA, antioxidant biomarkers in tissues homogenates and lung, brain and kidney function tests were performed. A

remarkable disturbance in tissues homogenates antioxidant status and lung, brain and kidney function tests were seen following administration of 1,2-dichloroethane. While, dietary supplementation of curcumin as different treatments ameliorated the investigated biomarkers. It could be concluded that dietary supplementation of curcumin reduced toxicity sings of 1,2DCE on kidney, lung and brain, which were considered as the most targeted organs of 1,2DCE toxicity.

Keywords: 1,2- dichloroethane, Curcumin, Antioxidants

1. INTRODUCTION

Curcumin (diferuloyl methane) is the chief curcuminoid existing in turmeric, that accountable for its yellow color phenolic pigment (El-Bahr, 2015). Curcumin possesses various biological activities that including anti-inflammatory, antioxidant, anticarcinogenic, antimutagenic, anticoagulant, anti-infective effects and regulating cytochrome P450 (CYP) activity (Cheng et al., 2014). Moreover, it has therapeutic effectiveness and acceptable safety specification (Bahramsoltani et al., 2017) and various diseases therapy such as rheumatism, diabetic ulcers, anorexia, cough and sinusitis (El-Bahr, 2015). Numerous publications have described the protective effects of curcumin in experimental animals in contrast to ovarian intoxication caused by ionizing radiation, testicular damage induced by cadmium (Aktas et al., 2012), and testicular injury from metronidazole (Noorafshan et al., 2011) all implying the beneficial role of curcumin.

Sun et al., (2016) reported the synthetic halohydrocarbon 1,2-dichloroethane (1,2-DCE) as a chemical that is extensively manufactured throughout the world as the monomer in the production of polyvinyl chloride, as industrial solvent and as glue thinner. When 1,2-DCE is used as a thinner of industrial adhesives, it is rapidly evaporated through the air, therefore, workers that exposed to high concentrations inhaled 1,2-DCE vapors in workplaces. A study showed that inhalation causes acute and subacute poisoning in both workers and laboratory animals (Zhou et al., 2015). Earlier studies shown that 2-chloroethanol (2-CE), a metabolite of 1,2-DCE generated in vivo via microsomal CYP2E1, is more reactive than its parent molecule, and play an important role in the hazardous properties of 1,2-DCE (Zhang et al., 2011).

Data collected from China revealed that different poisoning cases induced by 1,2- DCE have occurred in the past 30 years (Liu et al., 2010). The most pathological changes were toxic encephalopathy and brain edema (Chen et al., 2015). Significant indications indicated that 1,2-DCE is metabolized via cytochrome P450 2E1 (CYP2E1) in the body, which is supposed to play a vital role in the mechanism of 1,2-DCE toxicity. For this reason, oxidative damage could occur during the metabolic process. CYP2E1 expression could be upregulated by substrates for the enzyme in both humans and animals Zhang et al., (2015).

The study aimed to is to discuss the effects of curcumin powder for the prevention, protective and treatment of oxidative induced by 1,2-dichloroethane on rats' organs (kidney, lung and brain).

2. MATERIAL AND METHODS

The principles and methodologies for the biological and biochemical analysis characterization techniques utilized in this study described.

Material

Chemicals

- Pure curcumin powder was obtained from California Gold Nutrition Company -USA
- 1,2-dichloroethane was purchased from BDH pure chemical (will obtain from El-Gomhoria com. Cairo, Egypt), with molecular formula $C_2H_4Cl_2$ and purity of > 99%. It used as chlorinated solvents in this study.

Animals

- Fifty adult male albino rats (weighing 120±10 g) obtained from Vaccine and Immunity Organization, Helwan farm, Cairo, Egypt.

Diet

- Standard diet was prepared from fine ingredients per 100 g according to Reeves et al(1993)
- 1,2dichloroethane applied as a single dose (313 mg/100g diet) according to Cottalasso et al (2011)

- Dietary supplementation of Curcumin was achieved by adding curcumin as 1.5 g/kg/diet according to Suryanarayana et al. (2005)

Experimental design

Rats were housed individually in mesh bottomed metallic cages under healthy environmental conditions. Water and diet were provided *ad-libitum*. Rats were divided into five groups (10 rats each) as following:

Group 1: served as normal control fed standard diet.
Group 2: (positive control) fed basal diet to which 1,2-dichloroethane is added as (313mg / 100 g diet) for 4 weeks.
Group 3: (Protective group) fed standard diet supplemented with curcumin as 1.5 g/kg/diet for 4 weeks , then 1, 2-dichloroethane was added to diet for further 4 weeks.
Group 4: (Preventive group) fed standard diet with curcumin as 1.5 g/kg/diet for 4 weeks along with 1, 2-dichloroethane for 4 weeks
Group 5: (Curative group) fed standard diet + 1, 2-dichloroethane for 4 weeks after that the diet supplemented with curcumin as 1.5 g/kg/diet for 4 weeks.

The experiment was approved by the Ethical Committee of Vaccine and Immunity Organization, Cairo, Approval number (163-18).

Biological evaluation

The consumed food and body weights of rats were recorded twice a week to record feed intake and % change in body weight

- Feed intake was calculated as g /day/rat.
- % Body weight Change = Final body weight – Initial body weight/ Initial body weight X100

Biochemical analysis

At the end of experimental period, animals were fasted overnight for 12 hours then sacrificed under anesthesia using diethylether. Blood samples were obtained from hepatic portal vein and the rest of blood were left in centrifuge tube at room temperature for 15min and then centrifuged at 4000 r.p.m for 15 min. Serum was separated in plastic tube and kept at -20^{0}C until analysis.

Determination of oxidative stress biomarkers in organ homogenates

The internal organs (kidneys, brain and lungs) were excised, rinsed from blood in isotonic sterile saline, blotted dry and weighed then kept for biochemical analysis. In tissue homogenates, glutathione (GSH) was determined according to Beutler et al., (1963) and Superoxide dismutase (SOD) according to Beauchamp and Fridovich (1971). Malondialdehyde (MDA) was assayed as described by Uchiyama and Mihara (1978) in organs homogenate.

Determination of DNA, RNA and Total protein in brain tissues

Total protein was extracted from brain tissues and determined calorimetrically using BioMerieux kit. Nucleic acids (DNA and RNA were determined and total proteins were extracted from brain homogenate according to Shibko et al (1967).

Biochemical analysis in serum

Serum protein was determined according to Weissman et al. (1950) while serum urea, uric acid and creatinine were determined calorimetrically used BioMerieux kit. The serum cystatin-C levels and Serum neutrophil gelatinase-associated lipocalin (NGAL) were determined by using of Enzyme-Linked Immunosorbent Assay (ELISA) method, kits obtained from Biovendor -USA , while Nerve growth factor (NGF) was determined by ELIZA according to manufacturer instructions (Biocompare Kits , USA).

Statistical analysis

Statistical analysis of the results by using computer program statistical package for social science (SPSS); one-way analysis of variance (ANOVA) were used, the difference was considered significant at *P*-value < 0.05

3. RESULTS

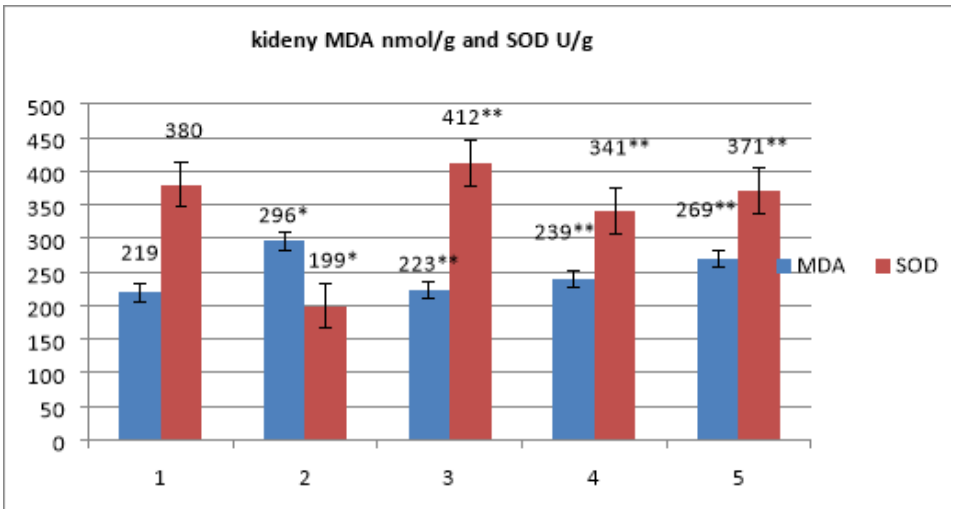
The concern of this study was to investigate the alteration the toxic action of 1,2-DCE by curcumin on rats' organs. However, no animal change behavior or mortality was found in experimental rats' exposure to 1, 2- DCE diet or any group.

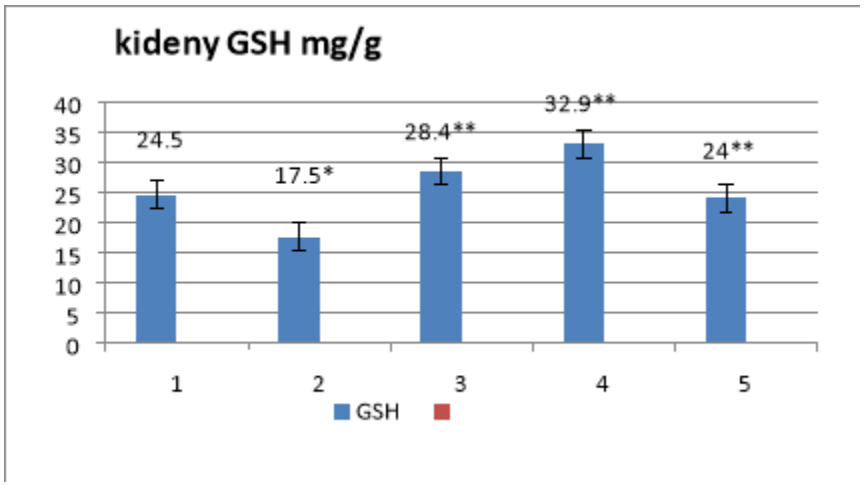
Table 1 Food intake and %body weight change as affected by curcumin with 1, 2- DCE

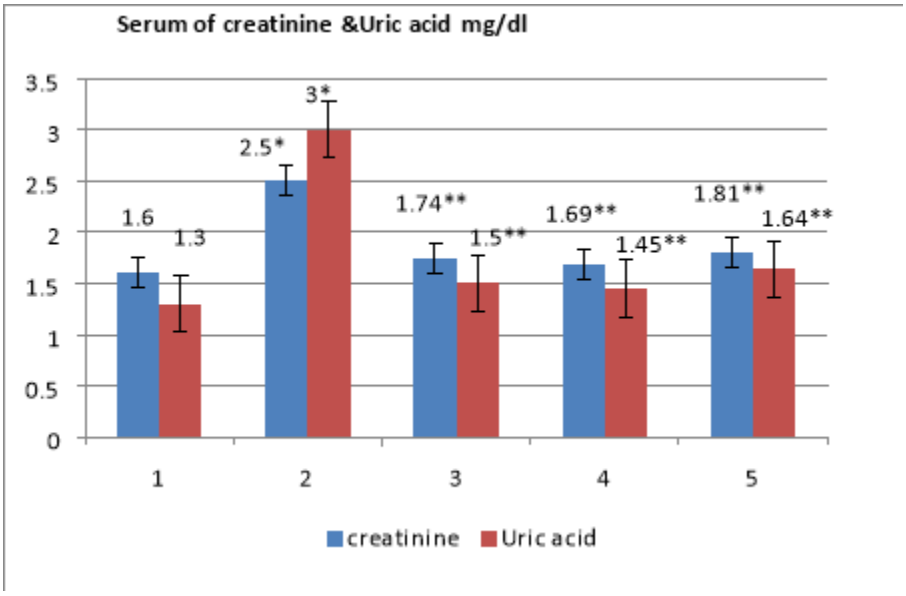
Groups / Parameter	-ve control G1	+ve control G2	G3	G4	G5
Food intake (g/ day/rat)	35.5±2.4	31.4±0.9*	35.1±1.7	33.6±2.0	32.3±1.5
% change of food intake	0.0	11.5	1.1	5.4	9.0
% Body weight change.	73.4±8.1	61.7±2.7*	73.3± 6.1**	67.9±6.6**	66.4±5.5**
% change	0.0	14.6	0.14	7.5	9.5

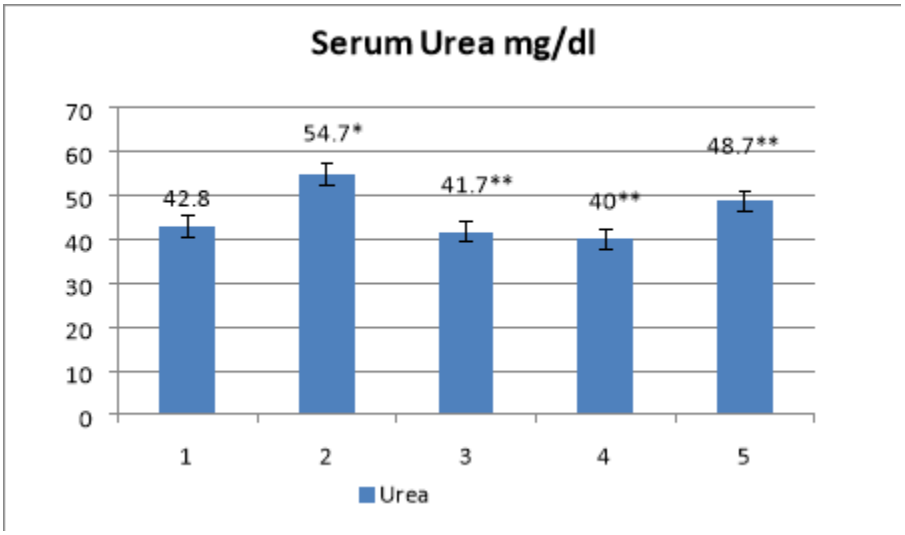
Significant difference from negative control *P<0.05

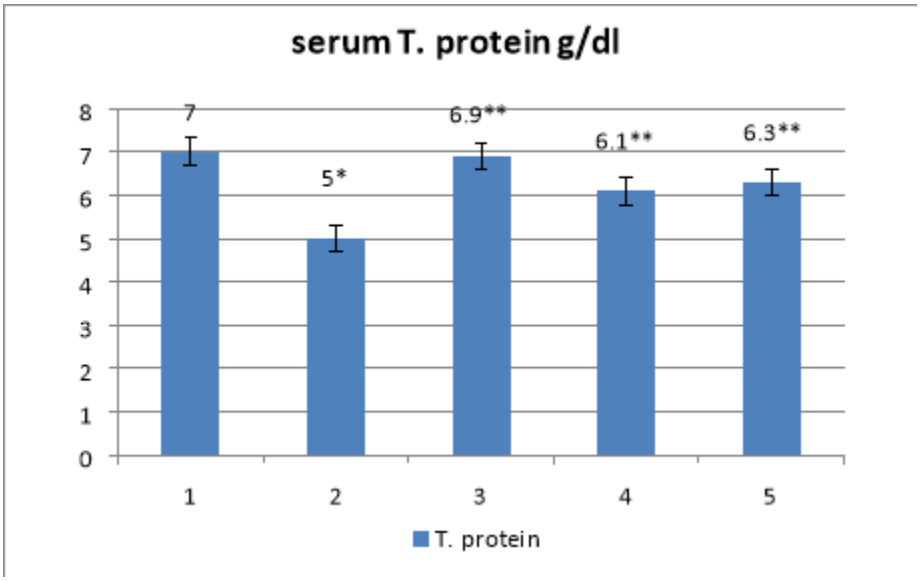
Results of table (1) illustrated that a decrease in food intake and change of body weight in all groups as compared to control group. Within treatment groups, the highest percentage of reduction was seen in G5 (curative group) as compared to control group (9.0% and 9.5% respectively) While G3 (protective group) was slightly decreased as compared to negative control group (1.1% and 0.14% respectively).

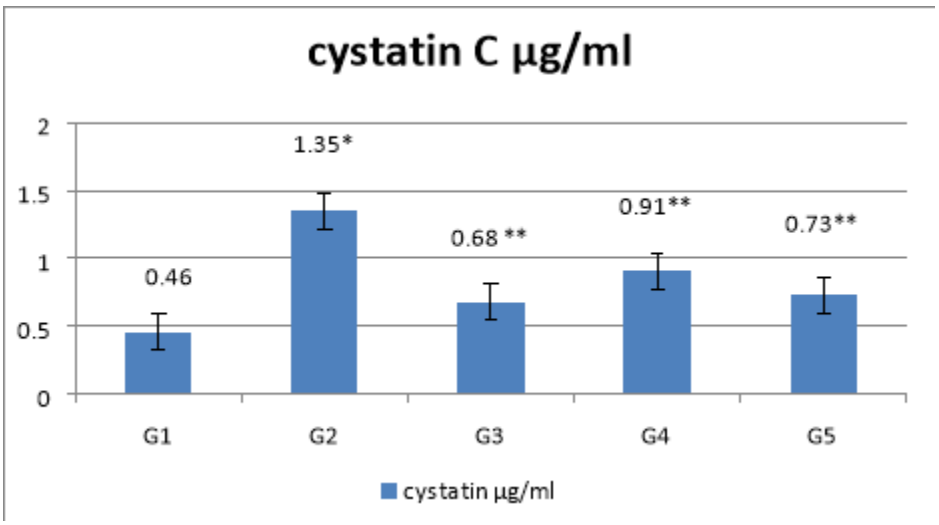


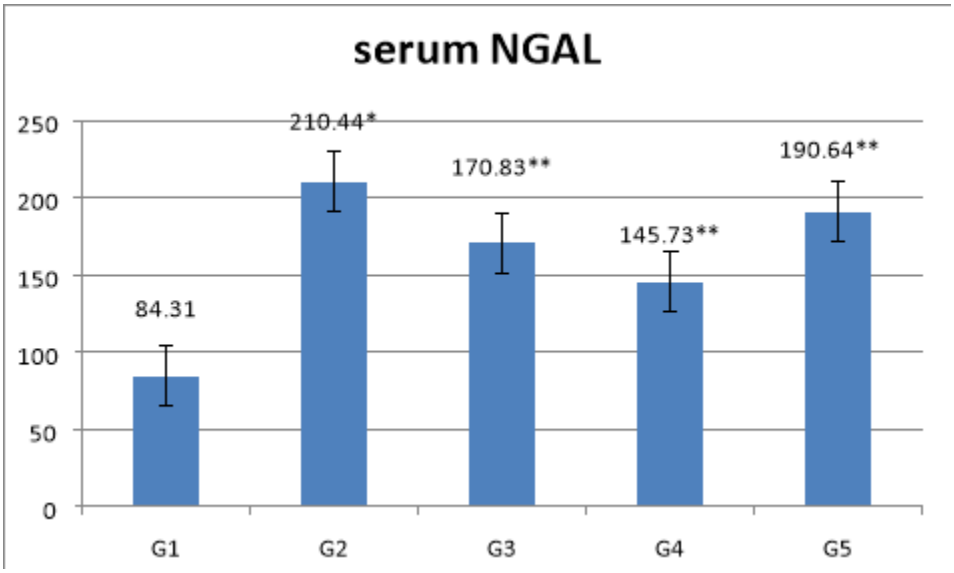








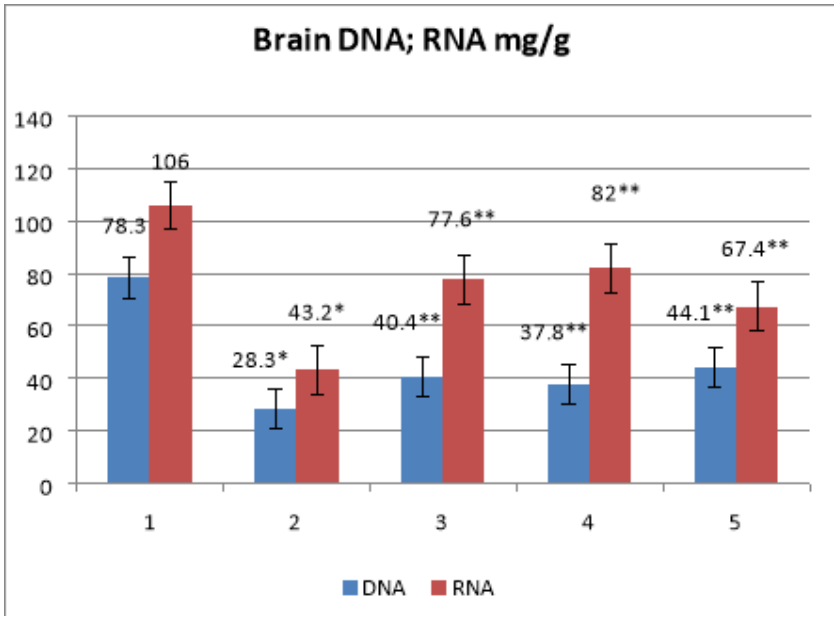


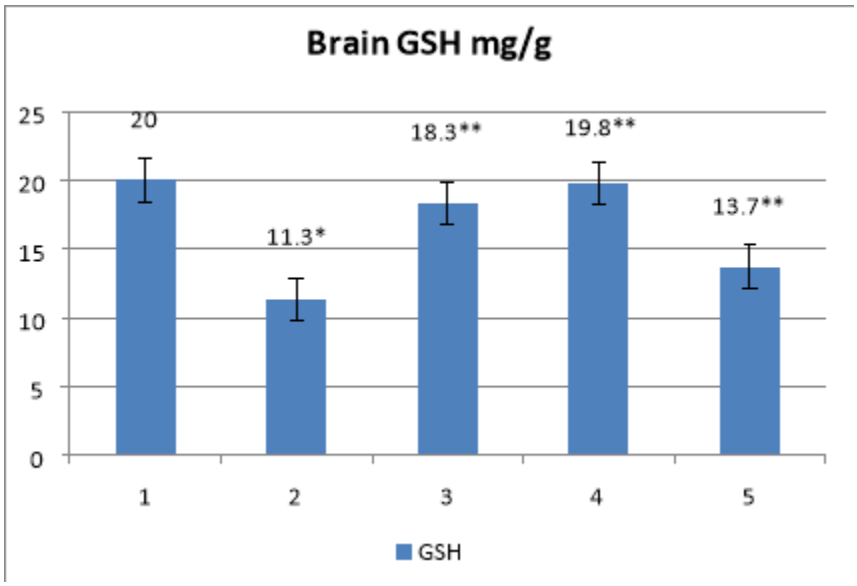


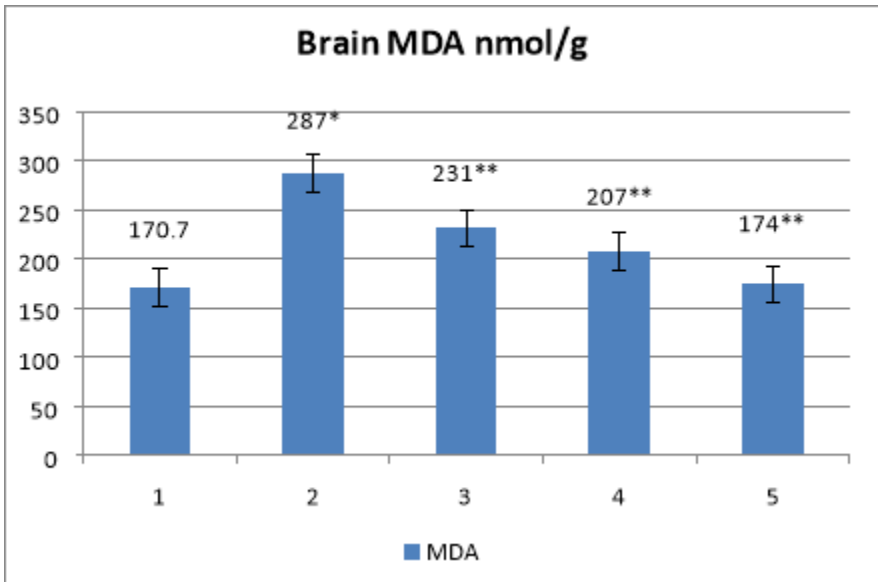
**means ±SD are significant (P<0.05) compared with normal control group (1),*
***means ±SD are significant (P<0.05) compared with Negative control group (2).*

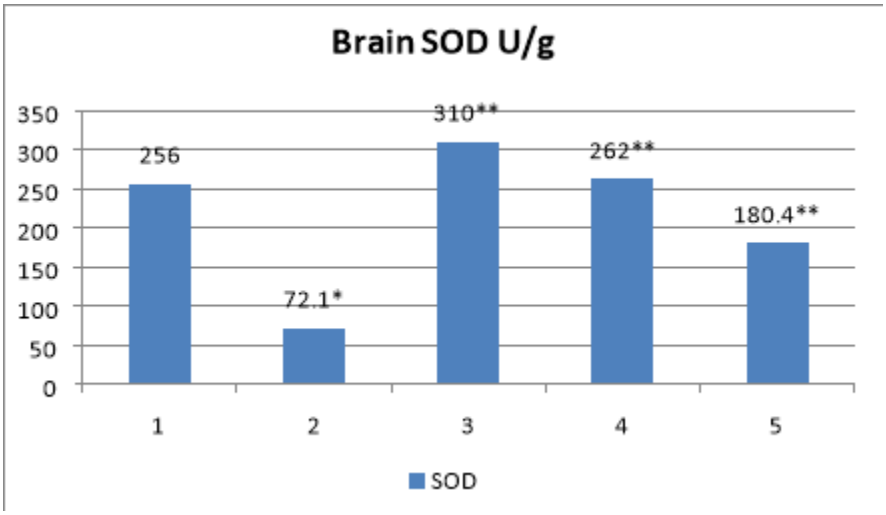
Figure 1 The effect of curcumin and 1, 2- DCE on kidney functions, oxidative status and Cystatin C in Kidney homogenate

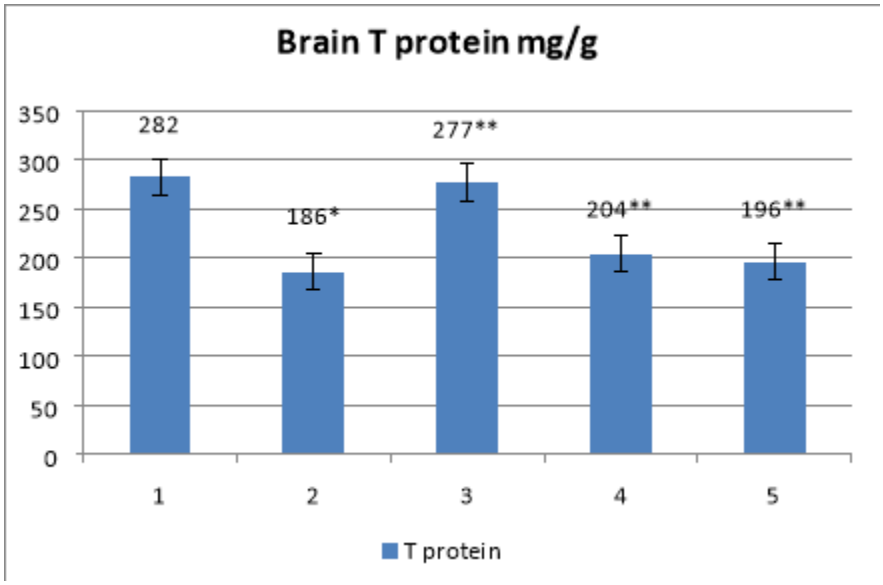
The present data in figure (1) showed the mean values of renal functions tests. Analyses of kidneys homogenate represents a significant reduction in GSH and SOD in positive group G2 compared to negative control G1, On the other hand, MDA levels has a significant increase in rat group G2 fed 1,2-DCE. Curcumin supplementation counteracted these results and brought them near normal levels.1,2 -DCE induced a significant reduction in serum levels of creatinine, urea, uric acid and a significant increase in total protein levels as compared with normal control group. Curcumin administration, as a protective agent G4, improved all kidney function parameters except total protein. Results revealed that, 1, 2- DCE increased serum level of Cystatin C significantly as compared to control rat group, meanwhile, using curcumin in treatment either as protective, preventive or curative group could reduce the elevated Cystatin C level significantly level. On the other hand, Results of serum NAGL showed that, 1, 2- DCE affects its level by inducing a significant increase as compared to control rats, in the same context, curcumin was has been claimed to reduce serum NAGL in all treated groups. Best results were obtained in G4.

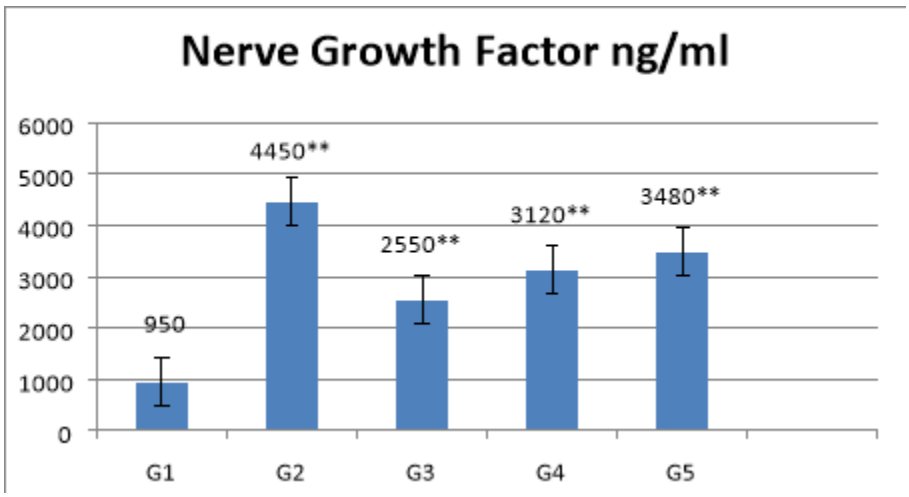










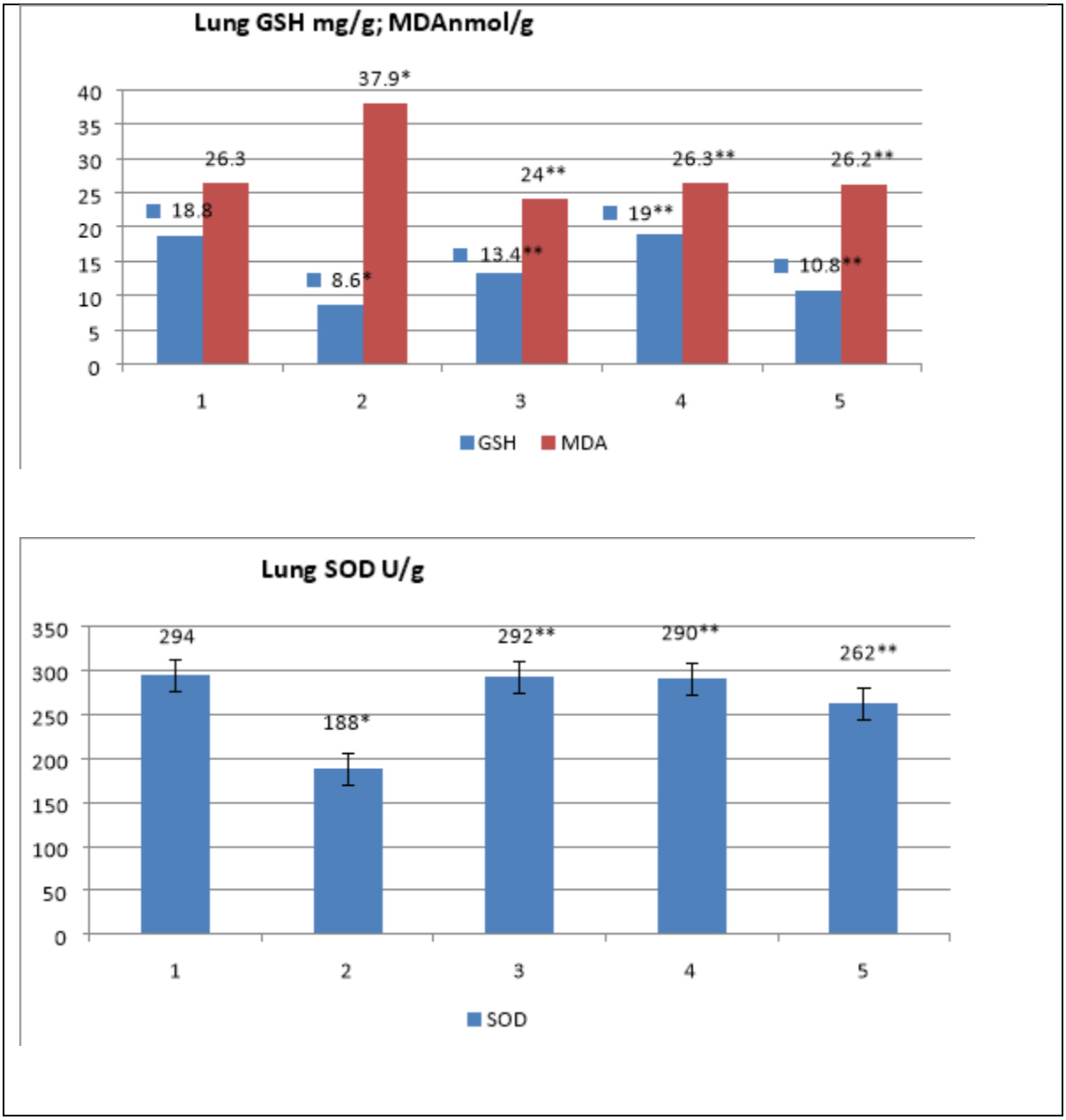


means ±SD are significant (P<0.05) compared with normal control group (1),

**means ±SD are significant (P<0.05) compared with Negative control group (2).*

Figure 2 The effect of curcumin and 1, 2- DCE on DNA and RNA contents, protein level, oxidative status and nerve growth factor in Brain homogenate

Data in figure (2) demonstrated the effect of 1, 2- DCE on brain tissue. Groups of rats fed chlorinated diet showed a significant depletion of intracellular GSH, SOD, DNA, RNA and total protein levels accompanied by a significant increase in MDA level in brain tissues as compared to normal control rats. Whereas, rat groups fed curcumin powder showed an amelioration of GSH was of G4 but MDA in G5 Results of SOD was higher than normal rats in both groups G4 and G5 as compared to normal rats (255.7 Vs 310.0 and 262.1). Compared with the normal rats 1, 2- DCE challenged rats displayed significantly high level of serum Nerve growth factor, which was then counteracted by curcumin treatment.



means ±SD are significant (P<0.05) compared with normal control group (1),

**means ±SD are significant (P<0.05) compared with Negative control group (2).*

Figure 3 The effect of curcumin and 1, 2- DCE on oxidative status of Lungs homogenate

The results in figure (3) clarified the effect of chlorinated solvent and curcumin on lung tissues. Rat group G2 received 1, 2- DCE diet detected a significantly lower level of GSH and SOD and higher levels of MDA than normal control group. It was observed that levels of MDA and GSH in G4 was nearly as normal control rats while, Best results of SOD was seen in G3 rat group as compared to other treated rats.

4. DISCUSSION

1, 2- DCE toxicity is strictly connected with its metabolism. Different experimental studies of the past years indicated that, the biotransformation of this compound was mediated by the mixed function oxidase system.

In the present study, the reduction in body weight gain obtained in the present research (table 1) agreed with observation of Cabre et al. (2001) they found that, the body weight was significantly lower in chlorinated solvent treated rats than in control animals. This decrease related to the significant accompanied decrease in GSH levels in different organ tissues of rats. Martensson et al. (1990) stated the importance of GSH in the function and structural integrity of the gut, and those GSH deficient mice showed sever weight loss and diarrhea due to colonic mucosa degradation. Other explanation might be due to 1,2- DCE circulation and bio-transformation in more metabolites with toxic action.

Reactive oxygen species play a role in the pathogenesis of renal injury. 1, 2- DCE induced nephrotoxicity leading to a moderate proximal tubular damage, thus increase the concentration of creatinine, urea and MDA also decrease GSH (Ali, 2004). Another response receiving antioxidants may exhibit pro-oxidants properties and even worsen renal damage or may due to natural antioxidant which causes a significant increase in renal activates of total superoxide scavenger activity and decrease renal MDA, blood urea and creatinine. An improvement of phenomena was observed after the consumption of curcumin due to its high content of natural antioxidants. Cohly et al. (1998) reported that curcumin provide protection against oxidative stress in a renal cell line by inhibiting lipid peroxidation. However, curcumin improved creatinine clearance and decreased the elevated levels of serum creatinine and urea (Tirkey et al., 2005). The protective effect of curcumin against oxidative stress has also been reported in a study which examined in vitro renal effects of curcumin in cultured cells exposed to renal ischemia (Yu et al., 2016). Moreover, A study by Liu et al. (2010) revealed that Curcumin ameliorated albuminuria, pathophysiologic changes on the glomerulus, kidney MDA SOD levels in type 2 diabetic nephropathic rats.

Our results revealed that 1, 2- DCE increase serum NAGL and Cystatin C significantly, several investigators have examined the role of NGAL as a predictive biomarker of nephrotoxicity following contrast administration (Schaub et al., 2007). Results agreed with a cross-sectional study, in which subjects in the intensive care unit with established acute renal failure displayed a greater than 10-fold increase in plasma NGAL concentration and more than a 100-fold increase in urine NGAL concentration by Western blotting when compared to normal controls (Mori et al., 2005). Both plasma and urine NGAL concentrations correlated highly with serum creatinine concentrations. These results identified NGAL as a widespread and sensitive response to established acute kidney injury in humans. On the other hand, curcumin has been shown to significantly and dose dependently improve the renal dysfunction induced by 1, 2- DCE in rat kidney. Earlier study by Venkatesan et al. (2000) shown that curcumin pretreatment decreases ischemia reperfusion induced rise in serum creatinine levels in kidney confirmed the protective effect of curcumin against nephrotoxicity. Moreover Fan et al. (2017) reported that curcumin presented reno-protective effects in acute kidney injury, Another study by Tan et al. (2019) prove that Curcumin protects kidney from cisplatin induced acute kidney injury through maintaining macrophage phenotype.

Brain biochemical analysis indicates an oxidative-stress induced by 1, 2- DCE followed by improvement due to curcumin consumption. The decrease in nucleic acid synthesis was since 1, 2- DCE is chlorinated derivative that could bind with protein endoplasmic reticulum and inhibit the nucleus activity leading to the decrease in DNA, RNA and protein content (Ray et al., 2000). On the other hand, chlorinated solvent produces free radicals during absorption and metabolism, which may affect the per-oxidative changes in membranes and another cellular component including oxidative DNA damage (Sasaki et al., 1999). Glutathione is bound to high affinity sites in the cytosol and perpetually lost from sites such as the nucleus. The addition of antioxidants within chlorinated scavenges the free radicals, prevent lipid peroxidation, increase antioxidants protection and generate peroxides that may prevent spontaneously reaction with nucleophilic centers in the cell. Antioxidants intakes increase the antioxidants level in brain and protect it against delayed cell death caused by free radicals (Rani et al., 2018). Also, curcumin could apply antioxidative properties as a chemical antioxidant of high ability to scavenge reactive oxygen species (Wang et al., 2014), and nitrogen free radicals (Trujillo et al., 2014). Results of nerve growth factor NGF indicate the damaging effect of 1, 2- DCE on brain tissues, a reduction in NGF levels was observed following curcumin treatment. The role of curcumin in promoting nerve repair has been increasingly identified in both central and peripheral nervous system. It was reported that curcumin could accelerate spinal cord repair and neural function recovery (Yaun et al., 2015). Specifically, curcumin has significant effects in cortical and sub-cortical regions including the medial prefrontal cortex (Noorafshan et al., 2017).

Lipid peroxidation is a public pathogenic mechanism of different toxic agents, including solvents (Durak et al., 2002). According to oxygen free radical theory, the intensity of this process is depending on the antioxidant enzyme level in the pulmonary tissue (Wargovich, 2006). The results showed a reduction in GSH and SOD and an increase in the content of MDA in lung tissues in rat

group fed 1, 2- DCE diet. This observation consistent with the mechanism described above and the enzyme activities are also elevated. This finding agreed with Salovsky et al. (2002) they found that a single dose (136mg/kg) of 1, 2- DCE caused toxic injury of rats' lung. Curcumin ameliorated the 1,2- DCE toxic effect on lung by reducing the lipid peroxidation and increasing both GSH and SOD. A study by Yaun et al., (2017) shows that curcumin can prevent restraint stress–induced oxidative damage in the brain, liver and kidney of rats .These results were nearly similar to Li et al., (2014) who illustrated that, a significant efficiency of curcumin was present in the initial phase of advancing inflammation, and the late persistency of elevated MDA concentration suggested a breakdown of the defensive potential. Also, Wang et al., (2014) reported that, curcumin caused a significant decrease the value of MDA concentration. Venkatesan and Chandrakasan (1995) described that curcumin inhibited the production of acute lung injury.

5. CONCLUSION

1,2 dichloroethane administration induces oxidative stress in rat organs as demonstrated by disturbance in oxidative parameters in different organ tissues, alterations in brain content of DNA and RNA and increase in brain and kidney function parameters. Dietary supplementation of curcumin improved the oxidative status of different rat organs.

Conflict of interest

Author declared that no conflict of interest.

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