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Ameliorative effect of curcumin on the toxicity induced by bisphenol A on brain of male albino rats

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Abstract: This study evaluates the effect of curcumin on the toxicity induced by bisphenol A on brain in male albino rats. Male rats (40.0±10.0 g) were divided into six groups of ten animals each group. Group 1 served as control, group 2 supplemented with curcumin, group 3 supplemented with BPA at dose 20 mg/Kg/day, group 4 supplemented with BPA at dose of (20 mg/Kg/day) with curcumin, group 5 supplemented with BPA at dose of (100 mg/kg/day) and group 6 supplemented with BPA at dose of (100 mg/kg/day) with curcumin for 6 weeks. The results showed significant changes in brain parameters. Supplementation of curcumin as antioxidant improves the activity of the enzymes superoxide dismutase (SOD), catalase (CAT), Glutathione-S-transferase (GST), glutathione peroxidase (GPx) and glutathione reductase (GR), and decrease in the activity of the enzymes xanthine oxidase (XO), and malondialdehyde (MDA) level in BPA treated groups. The results point to that curcumin is a powerful antioxidant has ameliorative effect against changes in antioxidant enzymes and oxidative stress biomarker in rat brain.

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1. Introduction

Bisphenol A (BPA) is a precursor industrial chemical that is widely used in the production of consumer products, including polycarbonate plastics, epoxy resins, and thermal paper. World-wide production of BPA has grown steadily over the past several decades, with greater than 10 billion pounds produced each year. This growth in production has contributed to the ubiquity of BPA in consumer products and in the air, soil, and water. As a result, human exposure through inhalation, ingestion, and/or absorption has resulted in circulating levels of BPA in the10–100 nM range(Gassman 2017).

Prenatal BPA exposure affects brain development, sexual differentiation, social and anxiety-like behavior, and learning (or) memory. In humans, emerging evidence for BPA-associated disruption to neurodevelopment is consistent with the rodent data and has revealed sex-specific effects of gestational BPA levels on emotional regulation and aggression in children (Geetharathan 2016). There is growing evidence that the induction of reactive oxygen species (ROS) by BPA may contribute significantly to its toxicity and carcinogenic potential (Rochester 2013; Seachrist, Bonk et al. 2016; Gassman and Wilson 2017)

The cells scavenge the ROS by antioxidants like glutathione-s-transferase (GST), glutathione peroxidase (GPx), superoxide dismutase (SOD), and catalase (CAT). In addition, exogenous antioxidants have helped these activities such as vitamins and flavonoids (Apaydin, Baş et al. 2017). Antioxidants usually interfere at one of the three steps including initiation, propagation and termination of the ROS mediated oxidative stress. Plant derived natural antioxidants like polyphenols and flavonoids have been widely reported for their free radical scavenging activity. Flavonoids can intervene and stop propagation by giving electron to peroxyl radical. Similarly, phenolic compounds have capability to inhibit enzymes and form chelates with trace metals; thus, they scavenge and suppress formation of reactive nitrogen species (RNS)/ROS and up regulate the antioxidant defense (Kazmi, Majid et al. 2018).

Curcumin is the principal curcuminoid of the popular Indian spice turmeric, which is a member of the ginger family, *Curcuma longa* L. (Zingiberaceae). Apart from culinary use, turmeric has been used in traditional medicine for the treatment of jaundice and other disorders of liver, parasitic infections, ulcers, inflammation of joints, various skin diseases, etc. Curcuminoids are a mixture of several structurally close phenolic compounds present in the rhizomes of turmeric. Three curcuminoids of major occurrence are curcumin (60–80%), demethoxycurcumin (10–20%),

and bisdemethoxycurcumin (5–10%) (Ghosh, Ghosh et al. 2011).

Curcumin has been shown to exhibit several activities including antioxidant, antimicrobial, anti-inflammatory, antiviral and anti- carcinogenic (García-Niño and Pedraza-Chaverrí 2014). Antioxidant and anti-inflammatory properties are the two primary mechanisms that explain the majority of the effects of curcumin. Curcumin has been shown to improve systemic markers of oxidative stress (Sahebkar, Serban et al. 2015). There is evidence that it can increase serum activities of antioxidants such as (SOD) (Banach, Serban et al. 2014; Panahi, Alishiri et al. 2016). A recent systematic review and meta-analysis of randomized control data related to the efficacy of supplementation with purified curcuminoids on oxidative stress parameters indicated a significant effect of curcuminoids supplementation on all investigated parameters of oxidative stress including plasma activities of SOD and catalase, as well as serum concentrations of glutathione peroxidase (GPx) and lipid peroxides(Sahebkar, Serban et al. 2015).

Curcumin has a wide spectrum of therapeutic properties. The presence of phenolic groups in the structure of curcumin is basic in explaining its ability to scavenge oxygen-derived free radicals responsible for the peroxidation of cell lipids (Apaydin, Aslanturk et al. 2019).

Curcumin's effect on free radicals is carried out by several different mechanisms. It can scavenge different forms of free radicals, such as reactive oxygen and nitrogen species (ROS and RNS, respectively) (Menon and Sudheer 2007); it can modulate the activity of GSH, catalase, and SOD enzymes active in the neutralization of free radicals (Marchiani, Rozzo et al. 2014); also, it can inhibit ROS-generating enzymes such as lipoxygenase/ cyclooxygenase and xanthine hydrogenase/oxidase. In addition, curcumin is a lipophilic compound, which makes it an efficient scavenger of peroxyl radicals, therefore, like vitamin E, curcumin is also considered as a chain-breaking antioxidant (Hewlings and Kalman 2017).

This work aimed to study the ameliorative effect of curcumin on the toxicity induced by BPA on brain of male albino rats.

2. Materials and methods

The experimental animals

Sixty young male albino rats Sprague-Dawley weighting 40.0 ± 10 g. The rats were obtained from the Holding Company for Biological Products & Vaccines (VACCERA), Helwan, Egypt. The rats were housed in plastic mesh cages for one week before the beginning of the experimental work that hang about for 8 weeks. The institutional animal care and use facilities from the Zoology Department, Faculty of Science, Tanta University-Egypt, approved the experimental design. Animals were fed on tap water supplied *ad libitum*. The temperature in the animal room was upheld at 25±3ºC with a relative humidity of 55±5% at the normal light-dark cycle. The experiment was done according to the National regulations on Animal Welfare and Institutional Animal Ethical Commttee (IAEC). Animals were carefully observed every day. Their body weights, food consumptions, and water intake were registered precisely every week to follow up any signs of toxicity or abnormality during the experiment.

The experiment

Rats were divided into five groups, each group of 10 rats. The Animals were given doses by stomach tube.

- Group 1: (control) Animals with normal diet.
- Group 2: Animals with normal diet and curcumin.
- Group 3: (low-dose BPA) Animals orally received low dose of BPA (20 mg/kg b.w.) (Kamel, Foaud et al. 2018).
- Group 4: Animals orally received low dose of BPA (20 mg/kg b.w.) with curcumin.
- Group 5: (high-dose BPA) Animals orally received high dose of BPA (100 mg/kg b.w.)(Kamel, Foaud et al. 2018).
- Group 6: Animals orally received high dose of BPA (100 mg/kg b.w.) with curcumin.

Methods

Tissue preparation

Brain, was immediately taken out, washed with ice cold saline to remove blood and tissue samples were homogenized in ice-cold phosphate buffer (50 mM phosphate pH 7.4) 10% (w/v) using Omni international homogenizer (USA) at 22,000 rpm for 20 s each with 10 s intervals. The homogenate was centrifuged at 2000 Xg in cooling centrifuge (Hettich, Germany) at 4ºC for 15 min and the supernatant was saved. The supernatant was freeze- thawed twice to complete mitochondria disruption (Salach Jr, 1978). Then the supernatant was again centrifuged at 6000Xgat 4 for 15 min and the yielded supernatant which contains the cystolic and mitochondrial enzymes was saved for immediate enzymes assays.

Enzymes and MDA were assayed by using Automated Elisa System Chemwell 2099 from Gama Trade Company. The research kits for application type of ELISA, Kamiya Biomedical Company (catalog no. KT-50849) was used for SOD assay activity, and (catalog no. KT-53246) was used for MDA level determination. The research enzyme kits for application type of ELISA, myBioSource (catalog no. 038818, 96 th) was used for CAT activity assay. The

research enzyme kits Bioassay Laboratory Technology for application type of ELISA (catalog no. E1172Ra) was used for GPx activity assay (catalog no. E0943Hu) was used for GST activity assay, (catalog No. E3495Hu) was used for XO activity assay.

Statistical analysis

Data were analyzed and represents mean±standard deviation (X±SD). Statistical comparisons were performed using one-way analysis of variance (ANOVA) followed by Dunntt's test to compare mean values between treatment groups and control. A value of $P \leq 0.05$ was considered as statistically significant using a computer program (Graphpad In State Software, Inc.).

3. Results

The effect of curcumin on the oxidative stress was clear in some parameters, and the result of six groups were represented in Figures (1-7). In figures the data were presented as six columns: control group, curcumin treated, low dose BPA treated group, low dose BPA with curcumin group, high dose BPA treated group and high dose BPA with curcumin treated group.

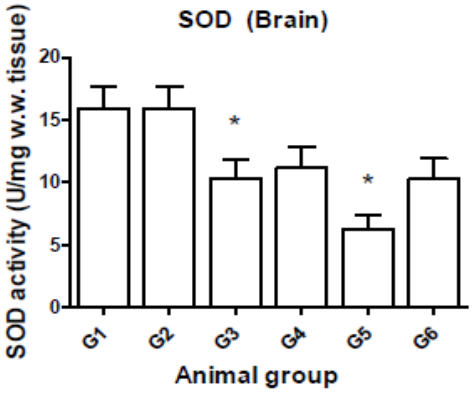
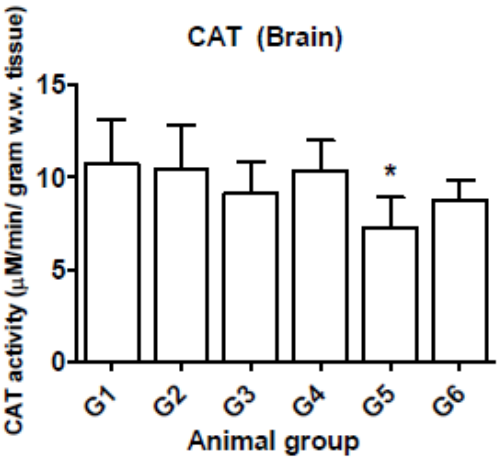


Fig. (1): Brain SOD activity of male rat



The activity of SOD shows significance decrease in groups 3 & 5 in comparison to control group. The activity of CAT in brain was significantly decreased in group 5 in comparison to control group. The activity of GST in brain showed significant decrease in groups 5 in comparison with control group. The activity of GPx in brain was significantly decreased in groups 3 & 5 in comparison with control. The activity of GR in brain was significantly decreased in groups 3 & 5 in comparison with control. The activity of XO in brain was significantly increased in groups 3 & 5 in comparison with control group. The activity of MDA in brain was significantly increased in groups 3 & 5 while no change in group 2 in comparison with control group.

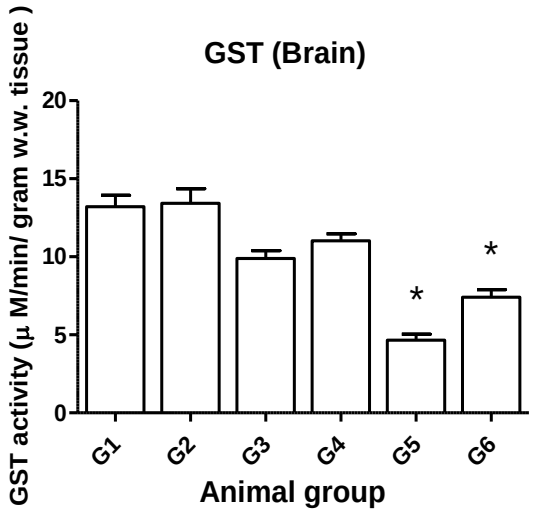


Fig. (3): Brain GST activity of male rat

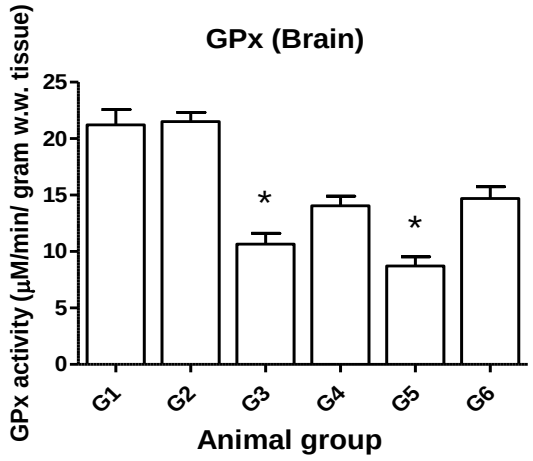


Fig. (4): Brain GPx activity of male rat

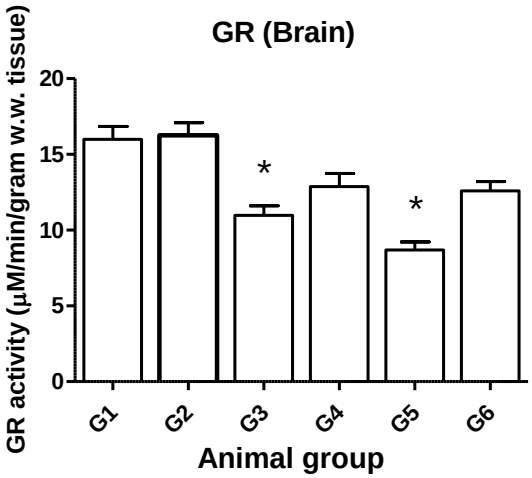


Fig. (5): Brain GR activity of male rat

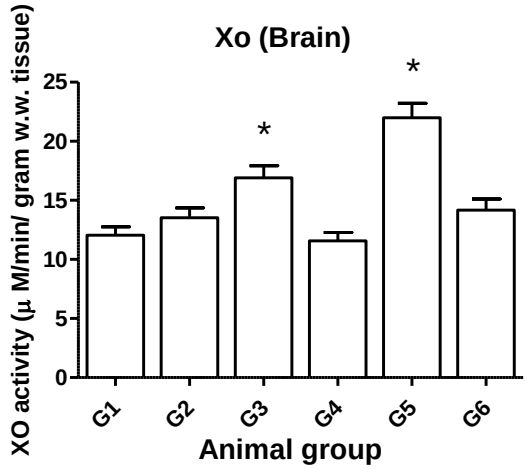


Fig. (6): Brain XO activity of male rat

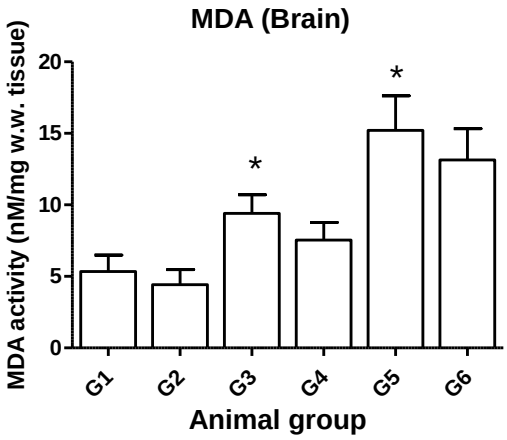


Fig. (7): Brain MDA activity of male rat

- Each reading represents mean ± SD of 10 rats.
- Asterisk indicates a significant increase in comparison with control at $p \leq 0.05$ determined using ANOVA followed by Dennett's test

4. Discussion

The activity of SOD, CAT, GST and GPx decreased and the level of MDA were significantly increased in brain of BPA-intoxicated groups (3 & 5) and this agrees with (Geetharathan 2016) who confirmed the same results as he studied the effect of bisphenol A on brain tissue of pregnant rat. Lipid peroxidation (MDA) activity was increased in BPA treated groups and this agree with (Jain, Kumar et al. 2011) who demonstrated that BPA induced cognitive dysfunctions and oxidative stress in rats as he showed that MDA level increase in BPA treated groups and the level was improved again when groups treated with N-acetylcysteine. And this agree with (Aydoğan, Korkmaz et al. 2008) who studied the effect of BPA, nonylphenol and octylphenol on brain tissue of male rats and found that administration of these chemicals decreased the level of GSH and increased the MDA, indicating oxidative damage in brain of rats on exposure to these chemicals.

Xanthine oxidase (XO) is a critical source of reactive oxygen species (ROS) in inflammatory disease as superoxide radicals and hydrogen peroxide (Kelley, Khoo et al. 2010). This enzyme catalyzes the oxidation of hypoxanthine to xanthine and can further catalyze the oxidation of xanthine to uric acid (Rajendran, Nandakumar et al. 2014).

Studies on XO have shown that modulation of enzyme activity, cofactor availability, substrate concentration and oxygen tension all affect rates of intracellular ROS production (Santos-Sánchez, Salas-Coronado et al. 2017). Although XO generates ROS, it should note that in vivo, the enzyme exists predominantly as dehydrogenase, reacting with NAD+. The present increase in the activity of XO may greatly contribute to an increased rate of ROS generation as result to the exposure of BPA.

Cells have many different mechanisms to protect themselves from oxidative stress and to fix up damaged biomolecules in cells. Within the methods, the cells used to do this; non-enzymatic and enzymatic antioxidants scavenge ROS, such as, SOD, CAT, or the glutathione peroxidase system, among others. The enzymes such as GPx, SOD, CAT, and GST play an important mission in preventing cells and tissues from oxidative damages (Baş, Kalender et al. 2015).

In this study, we showed that depletion of all antioxidant enzymes may result in oxidative stress. CAT scavenges H2o2 which generates free radicals (Eraslan, Saygi et al. 2007). Reduced CAT activity might be explained by reduced proportion of H2O2.

GST and GPx are cytosolic enzymes which detoxify various xenobiotics (Djuric, Begic et al. 2015).

We can say curcumin is non-enzymatic antioxidant, curcumin has a wide spectrum of therapeutic properties (Kim, Park et al. 2012). The presence of phenolic groups in the structure of curcumin is basic in explaining its ability to scavenge oxygen –derived free radicals responsible for the peroxidation of cell lipids(Rao 1994) and thus explain in the present study co-administration of curcumin resulted in significant improvement in antioxidant enzymes and decreased oxidative stress and this agree with other finding (Apaydin, Aslanturk et al. 2019) who discussed histopathological and biochemical studies on the effect of curcumin and taurine against bisphenol A toxicity in male rats.

The current results reflect the oxidant properties and ability of curcumin to scavenge the free radicals. Curcumin has protective effect for SOD, CAT, GPx, GST and GR activities that's decreased by BPA treatment. Curcumin decreases lipid peroxidation (MDA). These results agree with other finding (Elsayed, Hegazi et al. 2016).

Finally, it could be concluded that the present study indicated that BPA exposure can affect adversely in vital organs e.g., brain. The oxidative stress cause changes in brain parameters.

There is growing evidence that the induction of reactive oxygen species (ROS) by BPA may contribute significantly to its toxicity and carcinogenic potential (Gassman 2017).

The oxidative stress cause changes in brain parameters. And we need more herbal antioxidant in our daily routine.

Recommendation

Avoiding BPA is difficult, but not impossible. The National Institutes of Environmental Health Sciences (NIEHS) information on bisphenol A for providers and parents encourage providers to counsel families to prevent BPA exposure to reduce the potential risk of harm by:-

• Reducing the consumption of processed foods, increasing fresh and/or frozen foods, and reducing consumption of canned foods.

• Avoid the use of plastics with the recycling codes (often found on the outside bottom of containers) #3 and #7 because they can contain BPA.

• Use a vacuum machine that is fitted with a HEPA filter to get rid of dust that may contain BPA.

• Avoid microwaving polycarbonate plastic food containers. Polycarbonate is strong and durable, but over time it may break down from repeated use at high temperatures.

• Avoid washing polycarbonate plastic containers in the dishwasher with harsh detergents.

• When possible, opt for glass, porcelain, or stainless steel containers, particularly for hot food or liquids.

• Use infant formula bottles that are BPA free and look for toys that are labelled BPA free(Szaro, Hernandez et al. 2011; Sathyanarayana, Focareta et al. 2012)

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