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Monitoring of Low-Dose Effects of Bisphenol a on Superoxide Dismutase and Catalase Level in Female Rats

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ABSTRACT

Background and Objective: Inflammatory diseases are becoming increasingly prevalent worldwide, Exposure to environmental pollutants such as BPA could be one of the risk factors responsible for the development of such diseases. This study investigated the relationships between the serum levels of two endogenous antioxidants Enzyme and Bisphenol A concentrations. **Materials and Methods:** The study groups were divided into eleven healthy experimental animals. Serum Superoxide Dismutase (SOD) and Catalase (antioxidant enzymes), profiles were analyzed by spectrophotometric methods. **Results:** Serum Superoxide Dismutase (SOD) and Catalase (CAT) levels were significantly decreased in treated groups compared with control ($p<0.05$). **Conclusion:** This study demonstrated that the dose of BPA not only increases the free radical formation but also decreases its ability to detoxify ROS.

KEYWORDS

Superoxide Dismutase (SOD), catalase, bisphenol A, antioxidants enzyme, oxidative stressor, low-dose, Toxicity

INTRODUCTION

Bisphenol A (BPA) is a monomer used in the production of Polycarbonate plastics, it is also in many consumer products as lacquers applied as food can linings and coating on metal lids for glass jars and bottles[1]. Polycarbonate plastics are used to make a variety of common products used in food contact materials[2]. It is used in products like adhesive and flooring materials and paints and varnishes[3]. The BPA metabolism is dominated by phase II conjugation reaction in the hepato-intestinal tract[4] and it is removed from the blood by first-pass metabolism in the liver[5]. The main route of excretion is via faeces and urine[4].

Reports have shown that environmentally relevant doses of BPA can cause effects on human development and reproduction which include but are not limited to increases in weight and size of the prostate gland, decreases in sperm efficiency[2] and abnormalities in the oocytes[6]. Damage to the liver and kidney[7,8], DNA adduct formation[9], adipose tissue dysfunction[10], impaired plasma glucose[11] and recurrent miscarriage and birth defects[12].

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Low doses of BPA inhibit microtubule polymerization, affect the spindle apparatus and produce aneuploidy[2], congression failure, chromosomal misalignment and aneuploidy in oocytes[13], involved in insulin resistance[14], Synaptic abnormalities and recombination aberration in oocytes[15], metabolic/ endocrine dysfunctions[10], cancer and fertility problems[16] and alterations of various brain nuclear receptors, alongside, increased progesterone receptor immunoreactivity[17] and enhanced antagonism at thyroid receptors[18]. The BPA provoked an increase in body weight[19], spurring the formation and growth of fat cells[17], abnormal levels of the liver enzyme γ-glutamyl-transferases, alkaline phosphatase and lactate dehydrogenase[8,20]. BPA has adverse effects on testicular function[21] and it interferes with LH receptor-ligand binding[22]. Li *et al.*[23], reported reduced sexual desire, erectile or ejaculation difficulty and reduced sexual satisfaction. Rebai *et al.*[24], reported urinary BPA levels in workers of BPA manufacturing facilities In male species, researchers reported a decrease in steroidogenic enzymes[25,26]. Yang *et al.*[27], a study showed that circulating levels of inflammation factors were increased in response to BPA exposure. It has been shown that many environmental contaminants can induce oxidative stress, Chou *et al.*[28], showed that BPA can decrease the activity of antioxidant enzymes in the liver. Higher doses of BPA also provoked antioxidant activity[29]. Rashid *et al.*[30], showed oxidative stress BPA can cause oxidative stress by disturbing the redox status in cells[31].

This study aims to unveil/establish the possible effects and physiological disposition of bisphenol A on oxidative stress markers in female Wistar albino rats.

MATERIALS AND METHODS

Study area: The study was carried out at the Department of Biochemistry, Research Laboratory, Faculty of Natural and Applied Sciences, Gregory University, Uturu, Abia State Nigeria, from June to August, 2021.

Sample collection: Total 60 non-pregnant female rats of 5 weeks age were acclimatized in the laboratory for 7 days and randomly divided into 11 experimental groups of 5 rats each and respectively administered, 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9 and 1 mg of BPA/kg.b.wt./day. The first group which served as control did not receive any treatment but distilled water instead. The graded doses of BPA were dissolved in distilled water and administered by oral gavage using an intubation cannula (Lars Medicare Pvt., Ltd., new Delhi, India). Blood was obtained from the tail of the various groups by capillary action, weekly, after BPA administration for 13 weeks. Blood samples were processed for clinical assay.

Experimentation: Animals have housed in aluminium wire-mesh cages in a well-ventilated animal house with a 12 hrs dark/light cycle and at room temperature and were provided commercial rat pellets (Vital feed from Vital Group of Company, Nigeria) and water *ad libitum*.

At the end of the experiments, serum catalase and SOD were assayed using an Autochemical Analyzer (Lx 20 pro Autoanalyser, Beckman Coulter, Woerden, Netherland and Chemwell Chemical Analyzer, Manufacturer: Roche Hitachi, GMI.). All reagents were commercially obtained as already prepared kits. The kits for catalase and SOD were purchased from the Abcam United Kingdom. Individual tests were carried out according to the kit specifications.

Statistical analysis: Differences between obtained values (Mean±SD) were carried out by One-way Analysis of Variance (ANOVA) using SPSS software version 20.0 followed by the Tukey-Kramer Multiple Comparison Test. At $p \leq 0.05$ was taken as a criterion for a statistically significant difference.

RESULTS

Superioxide Dismutase (SOD): There is a significant decrease in the SOD activity in all the test groups when compared with the control at $p \leq 0.05$ (Fig. 1a-c). The activities fluctuate at various points of measurement (Fig. 1a-c). The observed decrease in SOD was consistent throughout the exposure.

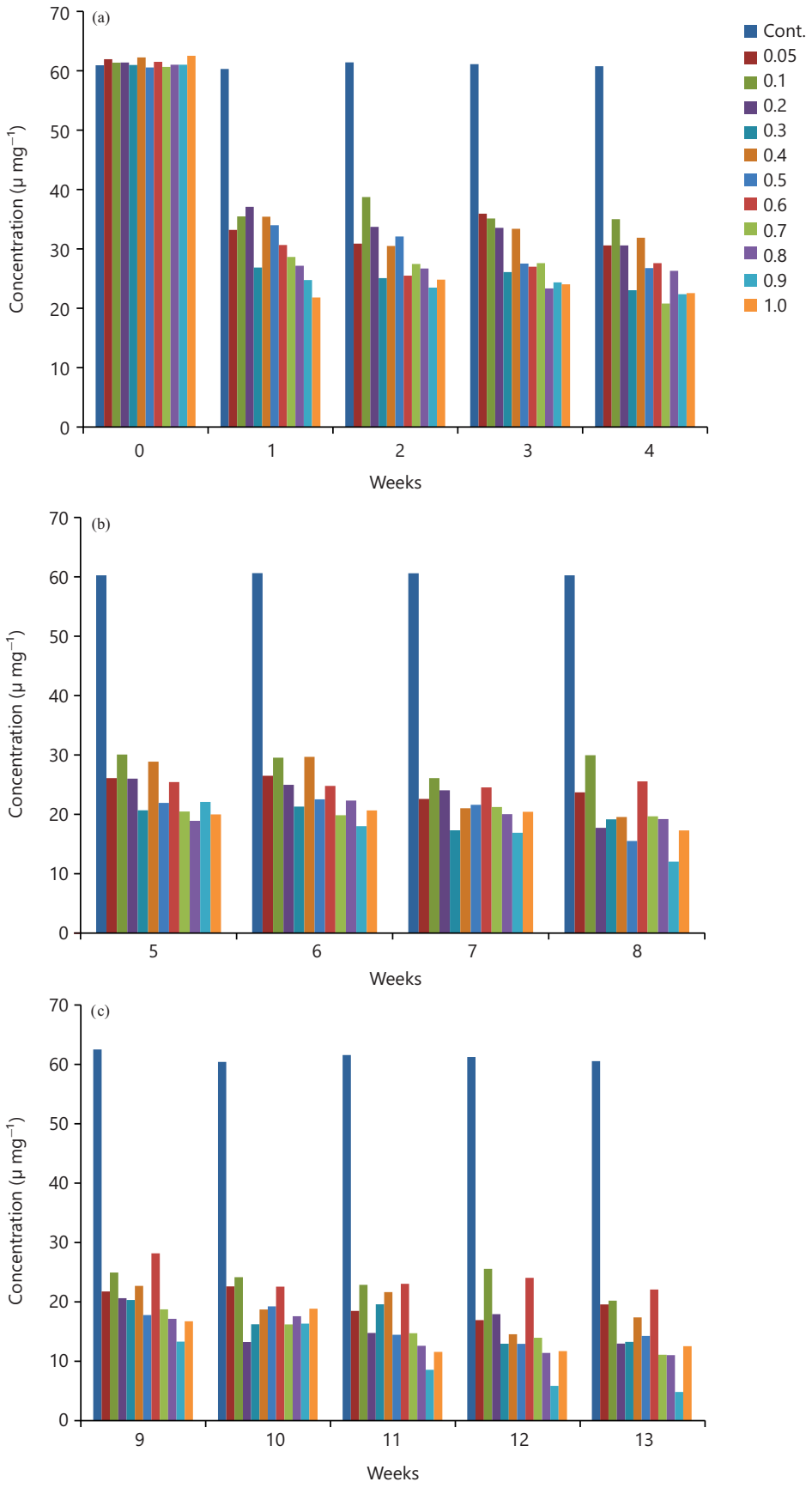

Fig. 1(a-c): Graph of Superoxide Dismutase (SOD) level, (a) Represents SOD activity after 1 month of BPA administration, that is from 1-4 weeks, (b) Following continuous administrations of BPA to the 2nd month (5-8 weeks) and (c) Showed SOD activity for the 3rd month of BPA administration (9-13 weeks)

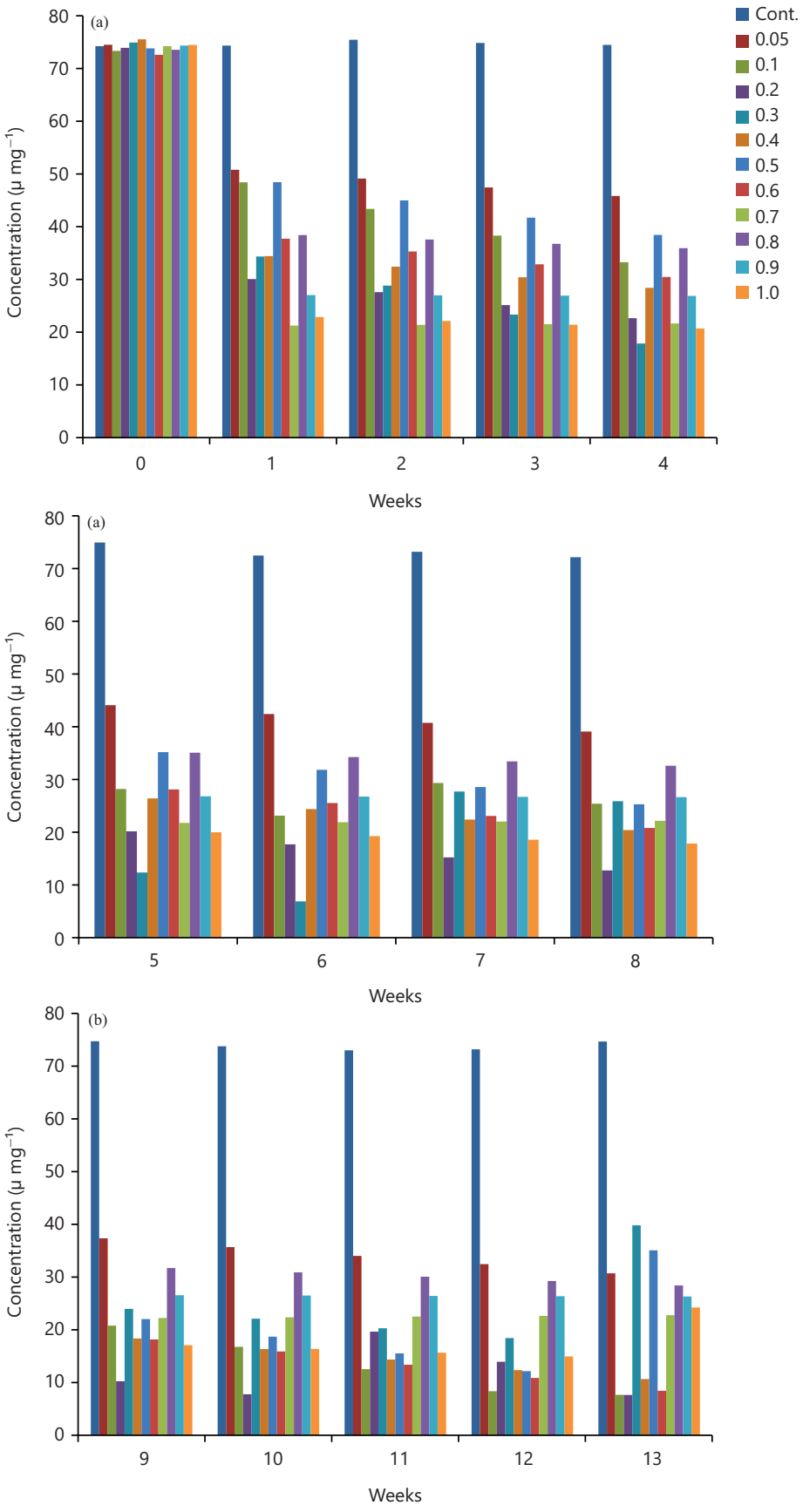

Fig. 2(a-c): Graph of catalase level, (a) Represents catalase activity after 1 month of BPA administration, that is from 1-4, weeks, (b) Following continuous administrations of BPA to the 2nd month (5-8 weeks) and (c) Showed catalase activity for the 3rd month of BPA administration (9-13 weeks)

Catalase: There is a significant decrease in the catalase activity in all the BPA-exposed groups when compared with the control $p \leq 0.05$ (Fig. 2a-c). The weeks of exposure varied across the groups (Fig. 2a-c). The group that received 0.9 mg kg^{-1} b.wt., of BPA showed a significant decrease in catalase that remain constant throughout the 13 weeks of exposure (Fig. 2c). Those that received 0.7 mg kg^{-1} b.wt., of BPA showed a significant decrease in catalase when compared with the control but non-significant variation from the 1st week to the 13th week (Fig. 2a-c). The other experimental groups revealed a significant decrease in catalase but interestingly also the catalase level decreases with an increased period of exposure to BPA (Fig. 2a-b), except for the 13th week of 0.3, 0.5 and 1.0 mg kg^{-1} b.wt., of BPA Administration, in which the catalase level tends to rise but not above the control (Fig. 2c).

DISCUSSION

The result of this experiment showed that there is a decrease in Superoxide Dismutase (SOD) and catalase. BPA induces Reactive Oxygen Species (ROS) production and significantly compromises mitochondrial function. The decrease in CAT activity increased the toxic effect of the free radicals formed from the BPA effect. Because BPA caused the induction of free radicals in the hepatic tissue, in consequence, it leads to disruption in the antioxidant defence system. It was found that BPA disturbs the balance of the mitochondrial antioxidant-pro oxidant status through the reduction of the activities of mitochondrial respiratory chain enzymes, which may cause mitochondrial dysfunction and increased ROS generation[32]. Additionally, it could be mediated through the ability of BPA to stimulate the polymorphism of oxidative stress-related genes[33]. The decrease in activities of the antioxidant enzymes might predispose the liver to increased free radical damage because CAT has been considered the primary scavenger of H_2O_2[34], SOD can catalyse the decomposition of superoxide radicals to produce H_2O_2. However, in absence of adequate CAT activity to degrade H_2O_2, more H_2O_2 could be converted to toxic hydroxyl radicals and may contribute to the oxidative stress of BPA, Which indicated liver tissue damage[35]. A high BPA dose tends to increase the free radical formation and decrease the cell's ability to detoxify reactive oxygen species[36]. The superoxide radicals and NO formation forms peroxynitrite as a result of high doses of BPA exposure leading to tissue damage and in turn, increasing the levels of NO[36,37].

Targets of oxidative stress include phospholipid membranes, proteins and nucleic acids. As such, increased systemic oxidative stress can lead to irreversible changes in these molecules as well as in mitochondria[38].

Following our finding, Hassan *et al.*[36], also show a decrease in SOD. Kourouma *et al.*[39], show a decrease in the activities of antioxidant enzymes, namely, CAT and SOD. Wu *et al.*[40], demonstrated significant decrease SOD. Hassan *et al.*[36], showed a decrease in CAT activity. Eid *et al.*[41], also demonstrated a decrease in the activities of antioxidant enzymes SOD and CAT. Aboul Ezz *et al.*[42], revealed a decrease the catalase activity. Abedelhaffeza *et al.*[43], observed decreased SOD activities in BPA administration. Chitra *et al.*[44], showed that the activities of superoxide dismutase and catalase, were decreased.

The reduced activity of catalase is linked to the depletion of the enzyme and enzyme inactivation caused by excess ROS production in mitochondria and microsomes[42] after BPA exposure. The observed decreased SOD activities, accompanied by the decreased CAT activities could be because of the metabolism of BPA in the liver, where it is glucuronidated by liver microsomes[45], mediated by UGT2B1, an isoform of UGT in rat liver. The metabolites of BPA produced by microsomal Cytochrome P450s enhance estrogenic activity[39]. Again, the mechanisms by which SOD can lead to increased cell death[46] and induced apoptosis is its ability to activate p53 by the production of H_2O_2[34] have been reported[46]. Also, another mechanism for SOD-. The reduction in the activity of catalase may be due to the exhaustion of the enzyme in attempting to eliminate the hydrogen peroxide generated after exposure to BPA. This may also be due to enzyme inactivation caused by excess ROS production in mitochondria and microsomes[47]. It was found that BPA disturbs the balance of the mitochondrial antioxidant-pro oxidant status through the reduction of the

activities of mitochondrial respiratory chain enzymes, which may cause mitochondrial dysfunction and increased ROS generation[32]. Additionally, it could be mediated through the ability of BPA to stimulate the polymorphism of oxidative stress-related genes[33].

This research implies that regardless of the presence of this antioxidant system, an over or unbalanced production of ROS due to contact with the chemical may result in several clinical disorders. With the growing epidemic of disease worldwide and the extensive use of consumer goods containing BPA, the risk of BPA as a potential triggering compound in disease must be examined.

CONCLUSION

There is increasing evidence that BPA is a toxic compound. However, the degree of toxicity depends on the dose, time, frequency, individual differences and age of exposure. The BPA is an endocrine disorderly chemical released in the environment, so most studies are focused on its effect on reproduction. Antioxidants reduce the cellular damage resulting from the interaction between lipid, protein and DNA molecules and ROS. Regardless of the presence of this antioxidant system, an over or unbalanced production of ROS due to contact with the chemical may result in several clinical disorders. With the growing epidemic of disease worldwide and the extensive use of consumer goods containing BPA, the risk of BPA as a potential triggering compound in disease must be examined. Many of the mechanisms known to exist in disease pathophysiology also appear to exist with immune reactivity from BPA exposure. In addition, severe oxidative stress resulting from early life exposure to BPA could lead to DNA damage and mutation of tumour suppressor genes. The cells have various defense mechanisms against oxidative stress, including enzymatic scavengers; that protect the system from the deleterious effects of ROS. The study revealed that BPA caused marked oxidative impact by decreasing the activities of antioxidant enzymes compared to their activities in the control group. This study demonstrated that a dose of BPA not only increases the free radical formation but also decreases its ability to detoxify ROS.

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