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Oxidative stress markers alteration by Bisphenol A exposure predisposes female albino rats to potential risks of oxidative injury

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Abstracts
Background: *All living organisms are constantly exposed to oxidant agents deriving from both endogenous and exogenous sources capable to modify biomolecules and induce damages. BisphenolA (BPA) is a long- and well-known environmental contaminant that is capable of causing free radicals generation by exerting oxidative stress. the imbalance between free radicals and antioxidant defence mechanism leads to modifications in tissue cellular membrane and intracellular molecules. In this research, the possible effects and physiological disposition of Bisphenol A on some oxidative stress markers in female wistar albino rats were monitored.****Methods:*** *11 experimental groups of 5 rats each were 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 bw/day respectively for 13 weeks. The control group did not receive any treatment, but distilled water instead. At the end of the experiments total antioxidant capacity, nitric oxide andnitrotyrosine were assayed spetrophometrically using anAutochemicalanalyser and commercially obtained already prepared reagent kits.* ***Results: t****he result of this experiment showed that there is a decrease in total antioxidant capacity while increase in nitric oxide and nitrotyrosine level was observed.* ***Conclusions:*** *BPA induces reactive oxygen specis (ROS) production and a significant increase in oxidative stress, which is accompanied by marked alterations in TAC*

keyword: *Bisphenol A, environmental contaminant, total antioxidant capacity, nitric oxide, nitrotyrosine, protein carbonyl, free radicals, oxidative stress.*

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I. Introduction

BisphenolA (BPA) is a long- and well-known environmental contaminant, that has been receiving a considerable amount of attention from the scientific community as well as the general public, mainly because of its ubiquity in our environment and uncertainties about its effects on humans. It is an organic compound with two phenol functional groups [1]. BPA molecules have a fairly strong fluorophore, weak chromophore and low sensitivity of UV detection[2]. Its loss process in the atmosphere is due to the rapid reaction with hydroxyl radicals and the photo-oxidation half-life for BPA in air is about 4hours [3]. Bisphenol A, no doubt is one of the world's highest production volume environmental chemical [4, used in the plastic and rubber industries, as plasticizer and as a polymerization inhibitor in polyvinyl chloride (PVC). BPA is a preferred colour developer in thermal paper [5]. BPA-based products are also used in foundry casting and for lining water pipes [6]. The global population is subject to repeated exposure to BPA, primarily through packaged food, drinking and bathing water, dental sealants, dermal exposure, and inhalation of household dusts [7]. BPA enters the body by the ingestion of contaminated food or beverages. It leaks from polycarbonate plastics, which are used to line food and drink containers such as bottles and cans. Further minor ways of penetrating into the body are through the skin [8] or inhalation [9].BPA accumulates in adipose tissue [10] and body fluids of the normal population.

BPA has been detected in the human placenta [11], cord blood [12], amniotic fluid[13][14], fetal liver [15] and breast milk [16][17], and in fetus [14].

Environmentally relevant doses of BPA can cause effects on human development and reproduction. Reports have shown that BPA causes; earlier puberty [18], trigers ductal and alveolar structures proliferations [19], development of ductal hyperplasia [20],modifications of the mammary gland architecture [21], mammary carcinogenesis [22], inflammatory cytokine dysregulation [23], and mitochondrial mediated apoptosis in the hepatic tissue [24]. Reported health implications associated with BPA exposure include diabetes [25], cardiovascular disease [26], altered liver enzymes activities [27] and obesity-promoting effects [28]. BPA induces oxidative stress [29], coronary artery disease [30],activates Maxi-K ion channels in coronary smooth muscle cells [31], increased BP and decreased heart rate [32], increased risk of hypertension [33], decreased efficiency of sperm production [29]and increased ovarian cancer cell proliferation [34]. several studieshavereported that absorption of BPA has cause extensive damage to the liver and kidney[35,27], induced the production of free radicals in hepatocytes [7]. BPA provoked an increase in body weight [28], and adipose tissue weight [36], alteration in adipogenesis and an increase in white adipose tissue and over expression of some adipogenic genes [29] and increase lipid accumulation in the differentiating adipocytes and upregulates the expression of adipocyte proteins through the activation of glucocorticoid receptor [19]. Environmentally relevant BPA levels has adverse effects on testicular function [37]and ovarian cysts [38]. It suppresses low glucose-induced intracellular calcium oscillation on α-cells *Ex vivo* [39], increase the activation of the transcription factor CREB [9], abnormal levels of the liver enzyme γ-glutamyl-transferases, alkaline phosphatase and lactate dehydrogenase [27, 25]. BPA exposure might perturb the neurotransmitter system [40]. BPA disruption of cytochrome P450 enzymes, Bodin*et al*[41] reveal increased sensitivity to cytokine-induced apoptosis in macrophages.It was reported that female and male health has been seriously threatened, and the environmental pollution was thought to be the main reason of this phenomenon [42]. BPA is a common environmental estrogen with endocrine Interference effect, and can affect multiple organs of human[43,44,45]. BPA affect the function of thyroid gland, disturb the internal hormonal environment [46], promotes a podocytopathy with proteinuria, glomerular hyperfiltration and podocytopenia [47]. As an environmental estrogen, BPA can affect the functions of reproductive system and lead to infertility [48], influence semen quality [49], decrease sperm count and quality [50] and DNA fragmentation in spermatozoa [51]. Although the body of ED research is continuously expanding, there still exist uncertainties in the process of BPA degradation in the body. It has been shown that many environmental contaminants can induce oxidative stress, according with this; Chou *et al*, [52], showed that BPA is able to decrease the activity of antioxidant enzymes and provoked an antioxidant activity [19]. A growing body of evidence shows higher BPA concentrations were associated with increased abnormal liver function tests [27,53]. BPA has the ability to generate reactive oxygen species (ROS) and reduce antioxidant reserves and enzymes that are critical for hepatic phase I and II biotransformation [54]. Similarly, others demonstrated that BPA generates ROS that causes oxidative damage in organs and tissues such as the brain, reproductive tract, and kidney of rats [55,56]. It was reported that BPA increases the generation of reactive oxygen species (ROS) and induced hepatic damage and mitochondrial dysfunction [57,58]. Therefore, exposure to BPA causes oxidative stress by disturbing the balance between ROS and antioxidant defenses system in liver [59]. BPA induces reactive oxygen specis (ROS) production and significantly compromises mitochondrial function. BPA can cause oxidative stress by disturbing the redox status in cells [60]. Bisphenol A being an endocrine disruptor, can mimick the body's own hormones and may lead to adverse health effects [61]. Yang *et al*[62] study showed that circulating levels of inflammation factors were increased in response to BPA exposure and Inflammation factors were also increased. Inflammatory diseases are becoming increasingly prevalent worldwide [63]. Exposure to environmental pollutants such BPA could be one of the risk factors responsible for the development of such diseases [64]. The aim of this study is to unveil/establish the possible effects and physiological disposition of Bisphenol A on oxidative stress markers in female wistar albino rats.

II. Materials And Methods

Study area: The study was carried out at Applied Biochemistry Lab, NnamdiAzikiwe University, Awka, Nigeria and Biochemistry Lab, Gregory University Uturu, Abia state, Nigeria from June -8September, 2018.

Methodology:

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 bw/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.

Animals were housed in aluminum wire-mesh cages in a well-ventilated animal house with a 12 h 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 total antioxidant capacity, nitric oxide, nitrotyrosine and protein carbonyl were assayed using anAutochemicalanalyser (Lx 20 pro Autoanalyser, Beckman Coulter, Woerden, Netherland andChemwell chemical Analyzer, Manufacturer: Roche Hitachi, GMI.). All reagents were commercially obtained as already prepared kits. The kits for total antioxidant capacity, nitric oxide andnitrotyrosine were purchased from Oxford Biomedical Research, Oxford, USA andAbcam 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.

III. Results

- **TOTAL ANTIOXIDANT CAPACITY**

There is a significant decrease in the total antioxidant capacity (TAC) level in all the test when compared with the control $p \leq 0.05$ (fig 1). The observed decrease in TAC showed in inverse dose dependent effect of BPA, as the TAC levels decreases with increases dose of BPA (fig 1). The TAC level of all the experimanteal group also showed a inverse time dependent reponse to BPA exposure, from week I to week 13. As the duration of exposure increases the TAC decrease, except for the test group 0.2mg/kg BPA that showed a different response where the TAC os week 12 and 13 increases relative to that of week 11.

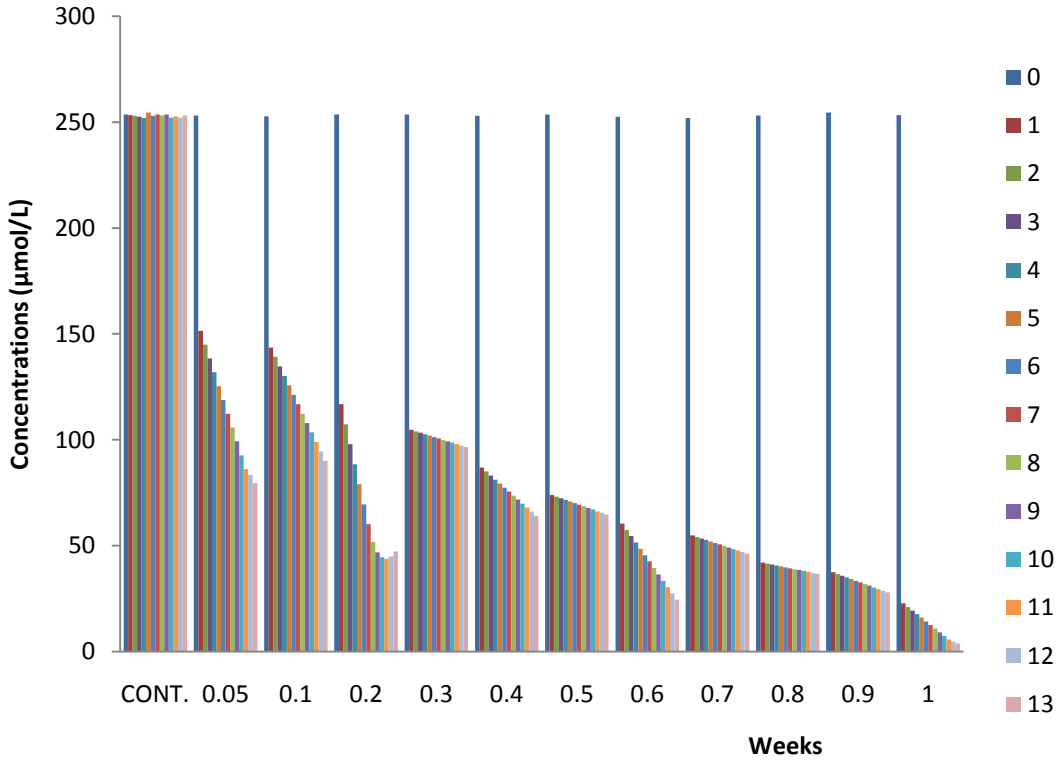

Fig. 1; Graph of total antioxidant capacity level.

- **NITRIC OXIDE**

There is a significant increase in the nitric oxide level when compared with the control at $p \leq 0.05$ (fig 2). At the onset of the experiment (week 1), the nitric oxide level in all the groups that were exposed to PBA were high with inverse exposure time relationship, as the duration of exposure increases, the NO level decreases with week 13 showing the lowest level of nitric oxide; an exception is the test group of 0.8mg/kg b.w BPA

where the NO level of week3 is high relative to weeks2 and 4. For test groups 0.05 - 0.2mg/kg b.w of BPA, the NO levels of weeks 11-13 falls below the week 0 NO level (fig 2).

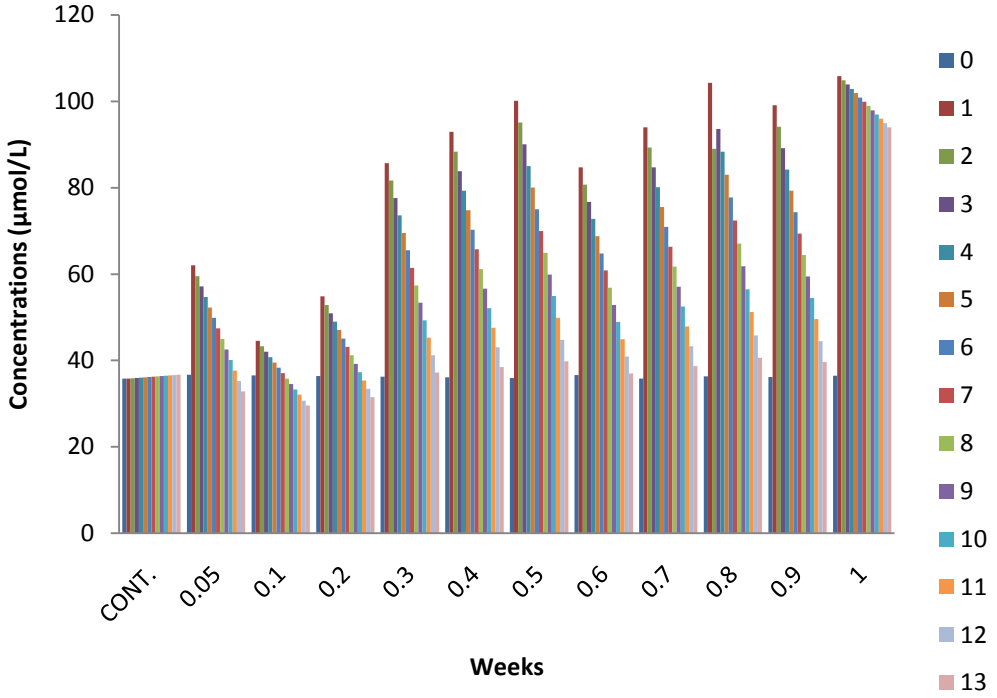

Fig. 2; Graph of nitric oxide level.

- **NITROTYROSINE**

There is a significant increase in the nitrotyrosine level in all groups when compared with the control $p \leq 0.05$ (fig 3). the nitrotyrosine level increases as the duration of the exposure toBPA increases (fig 3), except for the experimental groups that were given 0.3, 0.5 and 0.6mg/kg PBA that show relativel no difference across the duration of exposure.

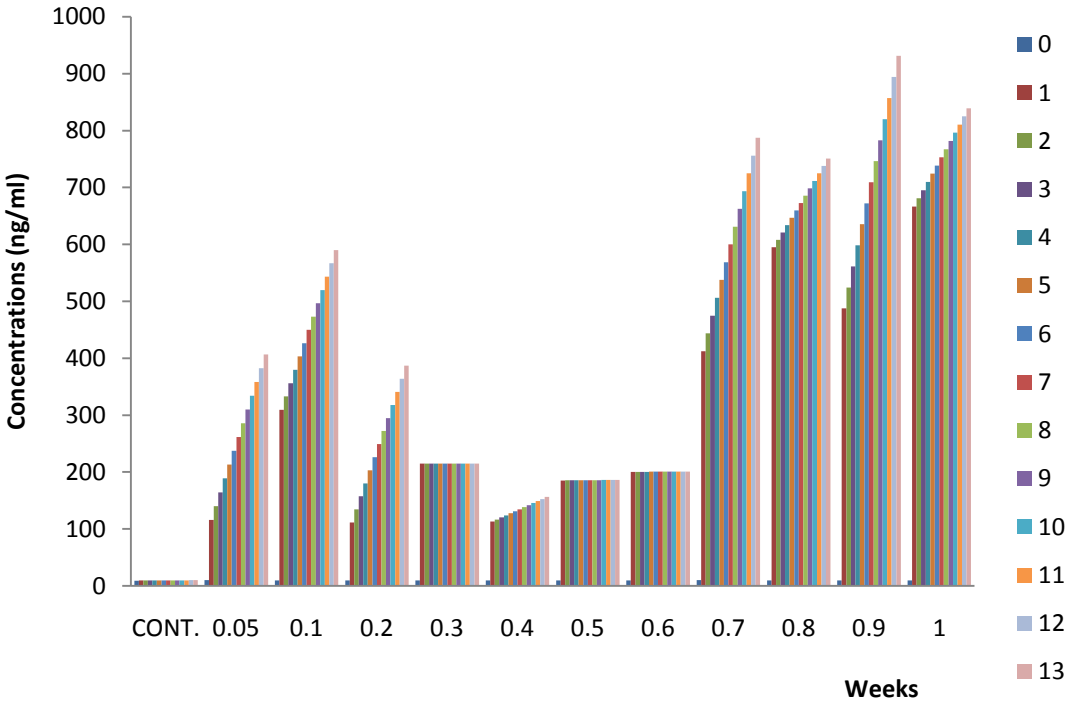

Fig.3; Graph of nitrotyrosine level.

IV. Discussion

The result of this experiment showed that there is a decrease in total antioxidant capacity while increase in nitric oxide andnitrotyrosine level. BPA induces reactive oxygen specis (ROS) production and significantly compromises mitochondrial function. BPA induced a significant increase in oxidative stress, which is accompanied by marked alterations in TAC [65]. Nitric oxide (NO) is a highly diffusible free radical. NO is a potent oxidant and nitrating agent is capable of attacking and modifying proteins, lipids, and DNA as well as depleting antioxidant defenses [66]. It may be postulated that the activation in NO levels induced by BPA administration may lead to the reduction in the rate and force of cardiac contractions [67]. Because BPA caused induction of free radicals in the hepatic tissue, in consequence, it leads to disruption in the antioxidant defense system. It was found that BPA disturbs the balance of the mitochondrial antioxidant-pro oxidant status through reduction of the activities of mitochondrial respiratory chain enzymes, which may cause mitochondrial dysfunction and increased ROS generation [68]. Additionally, it could be mediated through the ability of BPA to stimulate the polymorphism of oxidative stress related genes [69]. High dose of BPA not only increases the free radical formation but also decreases its ability to detoxify reactive oxygen species [54]. The formation of superoxide radicals together with NO might form peroxynitrite induced by high doses of BPA causes tissue damage leading to an increase in the levels of NO [54].With regard to nitrotyrosine, oxidized tyrosine moieties have been used to study pathways involved in oxidative stress after BPA exposure [70].Increased protein tyrosine nitration occurs during states that lead to high oxidant rates, such as inflammation. Importantly, several studies have shown that both oxidized tyrosines are associated with associated with a proinflammatory state, such as atherosclerosis [71], diabetes [72], lupus [73], and rheumatoid arthritis [74].

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 [75]. Elevated nitrotyrosine during pregnancy were found in perinatal asphyxia [76], and chronic hypoxia [77].An increase in nitrotyrosine was evident in both maternal and fetal sheep plasma in response to low BPA exposure. The low BPA dose induce postnatal systemic nitrosative stress in the adult. Importantly, the systemic nitrosative stress evident demonstrates that BPA exposure can disrupt oxidative stress pathways. The finding that BPA increased nitrotyrosine in adipose tissue of adult sheep and rats points to tissue-specific programming effects as well [78].

In accordance with our finding, [79]also demonstrated an elevated levels of NO and a decrease in total antioxidant capacity. Abedelhaffeza*et al*, [80] observed decreased TAC after BPA administration. Umbilical cord levels of nitrotyrosine were found to be high [81]. There is a positive correlation between maternal nitrotyrosine levels with cord nitrotyrosine levels [81] that maternal oxidative stress, specifically nitrotyrosine, The selective elevation in nitrotyrosine, evidenced in the current study suggests that BPA may enhance reactive nitrogen species through mechanisms that do not use myeloperoxidase such as peroxynitrite formation through direct reaction between superoxide and nitric oxide or through endothelial nitric oxide synthase uncoupling. Indeed, generation of nitrotyrosine by such mechanisms has been postulated in vasculopathy associated with diabetes, cardiovascular disease, and Fabry's disease [82]. Although some proteins and tyrosine residues are known to be preferentially nitrated [83].

V. Conclusion

BPA is an endocrine disorderly chemical released in environment, and antioxidants reduce the cellular damage resulting from 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 resulted in a number of 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. This study demonstrated that dose of BPA not only increases the free radical formation but also that BPA is a toxic compound,and its degree of toxicity depends on the dose, time,and frequency of exposure.

CONFLICT OF INTEREST: The author hereby declare no conflict of interest.
AUTHOR'S CONTRIBUTION: Chinenye E. Oguazu –analysis of TAC, NO, PC, N and result.
Francis C. Ezeonu – supervisor, Charles C. Dike and Anajekwu, B. Azuka- Animal experiment which includes feeding, administration of graded doses of BPA.
Charles G. Ikimi and Chinenye E. Oguazu – statistical analysis and result presentation
Ani N. Onuabuchi, Charles G. Ikimi and Nwobodo, O. Valentine - blood sample collection and processing.

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