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Protective roles of herbal teas against the toxicity of Bisphenol A on morphometry of uterus and improving murine reproductive health

Rasha Al-Eisa[1], Fatin Alsalmi[1], Rowa Kamal Zarah[1], Hamida Hamdi[1], Rokayya Sami[2]*, Suzan Abushal[3], Naseh Ateahallah Algehainy[4], Mohammad Alanazi[4], Faris Tayeb[4], Ahlam Abbas Harasani[5], Awatif Musallam Almehmadi[6], Noor Allehyani[7] and Abeer Ahmed Abu-zaid[8]

[1]Department of Biology, College of Sciences, Taif University, Taif, Saudi Arabia
[2]Department of Food Science and Nutrition, College of Sciences, Taif University, Taif, Saudi Arabia
[3]Program of Food Sciences and Nutrition, Turabah University College, Taif University, Taif, Saudi Arabia
[4]Department of Medical Laboratory Technology, Faculty of Applied Medical Sciences, University of Tabuk, Tabuk, Saudi Arabia
[5]Department of Biologial Sciences, College of Science, University of Jeddah, Jeddah, Saudi Arabia
[6]Department of Clinical Nutrition, Faculty of Applied Medical Sciences, Umm Al-Qura University, Makkah, Saudi Arabia
[7]Department of Medical Laboratories, College of Applied Medical Sciences, Shaqra University, Shaqra, Saudi Arabia
[8]Department of Food Science and Nutrition, Alkhurmah University College, Taif University, Taif, Saudi Arabia

Abstract: The purpose of the current study was to investigate the potential ameliorating murine reproductive effects of herbal tea extracts against bisphenol A-induced (BPA) cytotoxicity. A comparative study was applied among red, green, and blue teas in mice groups. Samples were coded as RTE, GTE and BTE groups, respectively. Several evaluations of murine reproductive were detected, such as diameters of uterine layers, pregnancy percentage, uterine, and offspring weights. The levels of malondialdehyde (MDA), oxytocin and cortisol were detected in plasma. The pregnancy percentage in the BTE + BPA group was 100% in the negative control group. The uterine weights of the mice groups with herbal teas ranged from 4.12g to 4.77 g. The offspring weights of litter from dams after exposure to BPA and various herbal teas ranged from 17.53g to 25.12 g and from 20.01 g to 28.19 g for females and males, respectively. The BPA toxicity exposure increased MDA levels to reach 19.18ng/ml in the BTE + BPA group as compared with the negative control group of 14.32ng/ml. The exposure to BPA toxins decreased the oxytocin level in the negative control group from 32.55ng/ml to 25.55ng/ml in the RTE + BPA group, while the cortisol levels reached 31.39ng/ml in the GTE + BPA group. The appearance of the luminal epithelial cells and endometrium in the BTE + BPA group was close to normal. It was indicated that herbal teas, particularly blue tea can be able to improve murine reproduction, while the harmful effects of BPA cannot entirely be mitigated.

Keywords: Toxicity, bisphenol A, uterus, mice, improving murine reproductive.

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INTRODUCTION

Tea is considered as the 2nd beverage after water. Herbal teas have become more widespread for avoiding the harmful effects of caffeinated drinks (Lakshan *et al.,* 2019). Herbal teas can be made from several types of flowers such as the butterfly blue pea, which has more antioxidant activities than green tea to protect the body from the free radicals damage (Ramli *et al.,* 2021). Blue tea is a caffeine-free tea that can be consumed in dry or fresh leaves (Minh, 2020). Blue tea is rich in catechin components which help in burning belly fat and losing weight with a calming effect and stress-relieving properties (Escher *et al.,* 2020). The consumption of blue tea can boost metabolism and consume extra calories (Kaewmanee *et al.,* 2011). The actual teas belong to *Camellia sinensis* and can vary into different types such as green, black, red and white teas. Green tea is a non-fermented tea that is well-known for its health benefits (Ohishi *et al.,* 2016). It can treat or even prevent several diseases, such as cancer, heart disease, diabetes and obesity (Chatterjee *et al.,* 2012). Green tea has plenty of essential components such as phenolics, flavonoids, and antioxidants which may positively affect the metabolic pathways (Maiti *et al.,* 2019). Fresh green tea contains multiple nutrients such as carbohydrates, protein, amino acids, minerals, vitamins, organic acids and small amounts of fat (2%) (Henning *et al.,* 2004). The catechin components in green tea are higher than in black tea which appeared on catechins, gallocatechins, epicatechins, epigallocatechins, epicatechin gallates and epigallocatechin gallates structures (Majumder *et al.,* 2022). The fully fermented process leads to the production of black or red teas with brothy and bitter tastes (Łuczaj and Skrzydlewska, 2005). Red tea is rich in alkaloids, flavonoids, carbohydrates, phenolic acids and amino acids (Vermeer *et al.,* 2008). It has multiple medical and pharmacological uses as it enhances brain

**Corresponding author:* e-mail: rokayya.d@tu.edu.sa

functions, memory, learning, nervous system and controls the level of serotonin and dopamine hormones (Leung *et al.,* 2001). Bisphenol A (BPA) is a chemical component usually used in plastic production due to its good properties (hardness, clear color andlightness) and coating on the insides of cans (Eladak *et al.,* 2015). BPA can be easily detected in human organs such as the fetal liver, cord blood, breast milk, and placenta (Huo *et al.,* 2015). BPA influence soxidative stress and pathogenesis for human and animal health (Zhang *et al.,* 2011). BPA overexposure plays an essential role in several diseases, alters the functions of the endocrine system and affects reproductive processes (Cousins *et al.,* 2002). Antioxidants and reducing agents such as herbal teas can protect from BPA toxicity (Nam *et al.,* 2010).

Therefore, the current research work aimed to investigate the protective roles of herbal teas against the toxicity of bisphenol A on the morphometry of the uterus and improve murine reproduction in mice.

MATERIALS AND METHODS

Herbal tea samples

Herbal tea samples and corn oil were purchased from the local market in Taif, KSA. Different tea samples were blue tea (*Clitoria ternatea*) red and green teas (*Camellia sinensis assamica*). Sample extracts were coded as BTE, RTE and GTE, respectively.

Aqueous extraction

The extraction of powdered tea samples was carried out by soaking 15 g of each type for 5 minutes in 500mL of boiled deionized water. The extracts were centrifuged at 10000 rpm for 10 minutes after cooling, while the supernatants were collected, freeze-dried and stored at -18 °C before and after mice testing.

Ethics approval and consent to participate

In the current experimental work was carried out under the Ethics Committee Number (8808/9988) at 2024 by Gulf Countries Association of Sciences in Animal Experimentation.

Animal study

Fifty healthy mice (*Mus musculus*) were randomly purchased from the vivarium of the Animal House in Jeddah, KSA. Females were 4 weeks old and about 25g (n=30), while males were 8 weeks old and about 35g (n=20). Mice were reared and housed under controlled environmental circumstances in separate stainless-steel cages with wood bedding. The condition was 25°C and 70 % humidity with a light cycle of 12 hours dark and 12 hours light. The mice had free access to clean water and a basic diet of 500g per cage weekly. Mice were subjected to 1 week of acclimatization before the experimental research.

Research design

BPA with a purity of 97% was purchased from Saudi Chemical Company, Jeddah, KSA. Mice were classified into 5 sets (10 rats each) and administrated as the following pattern: Group 1= (100mg/kg RTE + 5mg/kg BPA), Group 2= (100mg/kg GTE + 5mg/kg BPA) and Group 3= (100mg/kg BTE + 5mg/kg BPA). While Group 5 presents the (Positive Group (+)), mice were fed with a basic diet + 5 mg/kg BPA. Group 6 presents the (Negative Group (-)), mice were fed with a basic diet + 0.2ml/kg corn oil as the vehicle (Tyl *et al.,* 2002). The dose of BPA was calculated as (mg/kg) per body weight daily towards the murine models for 6 weeks. Mice were daily administered via oral gavage as described by (Akingbemi *et al.,* 2004).

Evaluation of murine reproductive processes

In a 1:1 ratio, five treated female mice were chosen to mate with fertile male mice. For five days, the pairings were housed in the same cages, while the number of pregnant female mice was noted. The pregnancy percentage was calculated, while the offspring weight for males and females was recorded after the 19^{th}-21^{st} day of gestation phase (Goh *et al.,* 2021).

Sample collection and medical evaluations

Daily body weights for mice were noted during the experimental period. On the final day of the experiment, the mice were anesthetized under a 40 mg/kg anesthesia injection of sodium dipyrone followed by the addition of 200 mg/kg in the drinking water. Blood samples were withdrawn and neatly collected from the heart, while the plasma was detected by centrifuging at 2000 rpm for 10 minutes and stored at -20°C for further analysis (Draper *et al.,* 1993; Baazeem *et al.,* 2024). The levels of malondialdehyde (MDA), oxytocin and cortisol were detected by ELISA kits (Sigma, CA, USA) (Draper *et al.,* 1993; Zaid *et al.,* 2018). The mice were sacrificed by using ketamine, while the whole uteruses were harvested and immediately weighed for the uterotrophic response evaluations as luminal epithelial cells' height, the thicknesses of endometrium, myometrium and perimetrium. Histomorphometry was performed on tissue-processed uterine sections using an image analyzer (NIS-Elements, Nikon, Japan).

STATISTICAL ANALYSIS

One-way analysis of variance was used to analyze each of the chosen parameters and the Bonferroni test (multiple comparisons) was then applied with SPSS Statistics 20 (IBM Corporation, Armonk, New York, USA). The data was presented as mean ± SEM. P less than 0.05 was deemed significant.

RESULTS

Effect of herbal teas on pregnancy percentage

The study of harmful biological effects on the reproductive system is known as reproductive toxicology

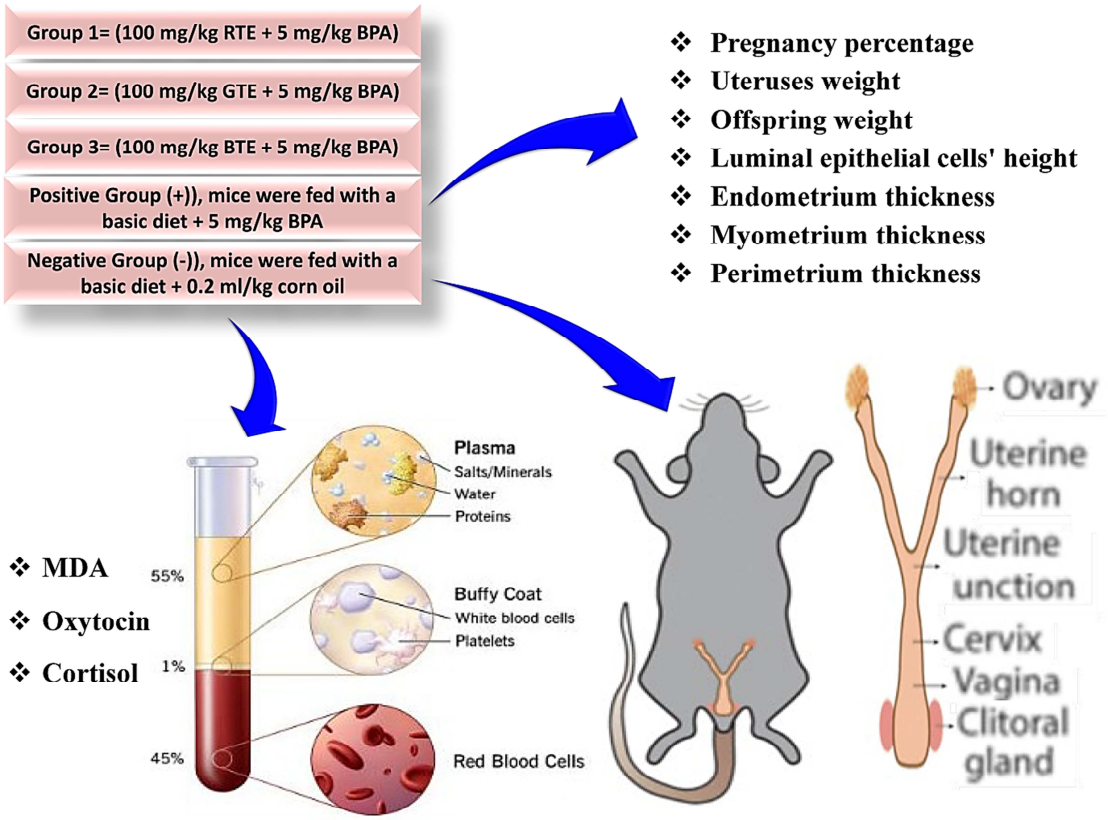

Fig. 1: Summary of the experimental processes

as a result of exposure to xeno-estrogenic substances such as BPA, which is present in infant formula and leaches from polycarbonate bottles (Biles *et al.,* 1997). As presented in fig. 2, changes in the pregnancy percentage were evaluated. The pregnancy percentage in the BTE + BPA group was 100% as the negative control group. BTE preserved the murine reproductive after exposure to BPA toxins compared with the RTE + BPA group and GTE + BPA group which reported 84.24 % and 97.59 %, respectively. Similar results were observed for the reduction in pregnancy percentage after exposure to BPA toxins (Ng *et al.,* 2021).

Effect of herbal teas on uterine weight

The effects of xeno-estrogen on the uterus are highly sensitive, particularly when an organ weight of ≥10% is taken into consideration (Vigezzi *et al.,* 2015). Different trends were detected for uterine weights. When the mice were given BPA toxics concurrently, the increase in uterine weight gain was reduced. fig. 3. The positive control group's reported uterine weight was 5.83 g, while the negative control group's was 4.78 g. The uterine weights of the mice groups with herbal teas ranged from 4.12 g to 4.77 g. BTE + BPA group treatment prevented the effects of BPA toxins.

Effect of herbal teas on offspring weights

BPA exposure can have a detrimental effect on male mouse offspring's ability to produce sperm during a crucial developmental stage (Chitra *et al.,* 2003). Fig. 4 presented the offspring weights for both females and males. The offspring weights of litter from dams after exposure to BPA and various herbal teas ranged from 17.53g to 25.12g and from 20.01g to 28.19g for females and males, respectively. The negative control group reported 16.23g and 15.98g for females and males, respectively. Results were in agreement with Rubin *et al.,* 2001) who studied the effect of BPA on several parameters such as offspring weights and estrous cyclicity patterns.

Effects of herbal teas on plasma levels of MDA, oxytocin and cortisol

The effect of various herbal teas on plasma MDA levels is presented in fig. 5. The BPA toxicity exposure increased MDA levels to reach 19.18 ng/ml in the BTE + BPA group as compared with the negative control group 14.32 ng/ml. The RTE + BPA group reported the lowest level of

MDA 14.83 ng/ml. The findings were in link with Sangai *et al.* (2014) who investigated the BPA toxicity in a mice model's liver and kidney. Plasma oxytocin levels are presented in fig. 5. The exposure to BPA toxins decreased the oxytocin level in the negative control group from

32.55 ng/ml to 25.55 ng/ml in the RTE + BPA group. While the BTE + BPA group increased plasma oxytocin level to reach 28.73 ng/ml. The results agreed with Wu *et al.* (2012) who reported the functional uses of antioxidants to reduce oxytocin levels. The exposure to BPA toxins increased the cortisol levels in plasma especially in the positive control group to reach 39.01ng/ml, fig. 5. The phosphorylation of CAMP response element-binding protein may be enhanced by endometrium and perimetrium with an increase in the myometrium thickness (8.77µm, 180.91µm, 10.13µm and 255.10µm), respectively. The negative control group detected normal uterine diameters and healthy endometrial glands. The RTE + BPA group reported an increase in the myometrium thickness with a reduction in oestrogenic action, leading to a rise in cortisol levels (Lejonklou *et al.,* 2010). The administration of herbal teas decreased the cortisol levels to reach 31.39 ng/ml in the GTE + BPA group.

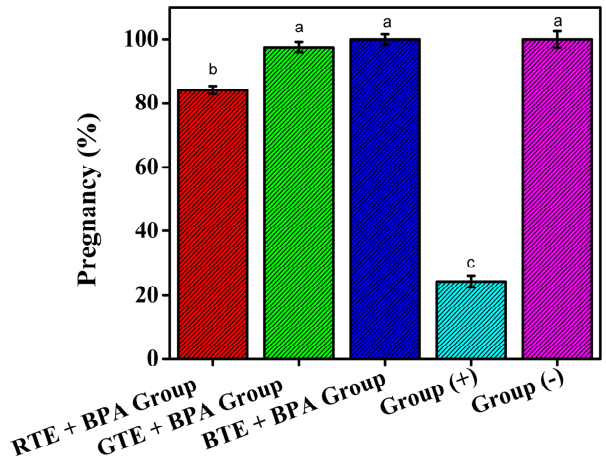

Fig. 2: Effect of Herbal Teas on Pregnancy Percentage among Mice Groups

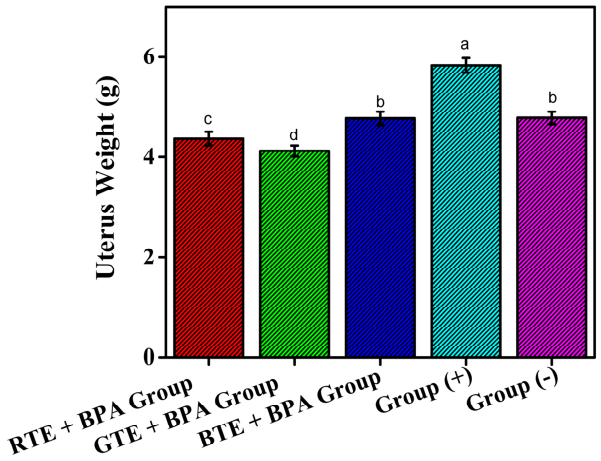

Fig. 3: Effect of Herbal Teas on Uterine Weight among Mice Groups

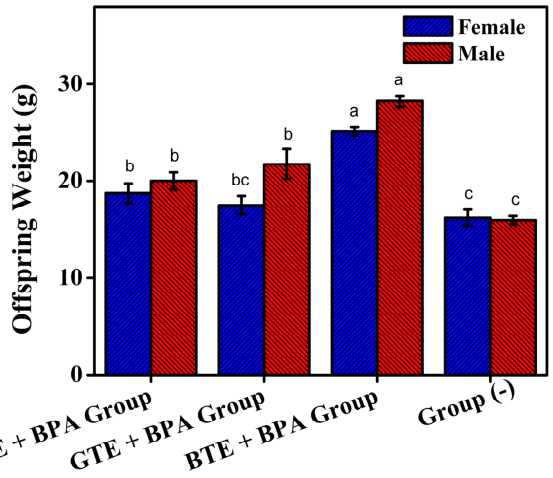

Fig. 4: Effect of Herbal Teas on Offspring Weights among Males and Females

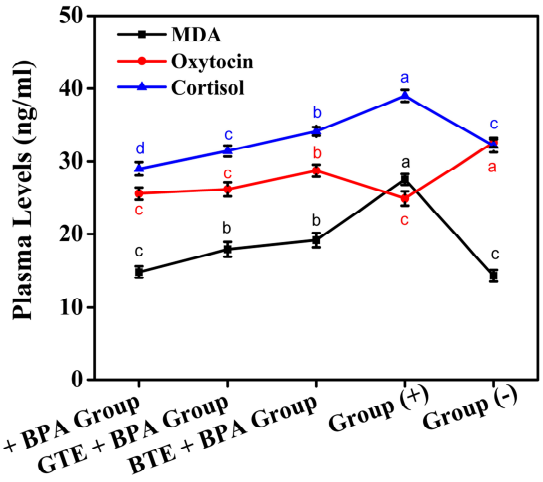

Fig. 5: Effect of Herbal Teas on Plasma levels (MDA, Oxytocin and Cortisol) among Mice Groups

Effect of herbal teas on the diameters of uterine layers

The effects of herbal teas on the diameters of uterine layers are presented in table 1. The positive control group exposed to BPA appeared unhealthy and shrunken resulting in a decrease in luminal epithelial cells' height and the thickness of various muscular uterine layers as luminal epithelial cells height and the thickness of endometrium and perimetrium (247.13µm 17.02µm 230.11µm and 12.59.10µm), respectively. Moreover, the appearance of the myometrium layer of RTE + BPA group was close to normal. The GTE + BPA group reported a reduction in myometrium thickness (233.95µm). BTE + BPA group reported an increase in luminal epithelial cells height and the thickness of endometrium and perimetrium (18.57µm, 244.11µm and 14.55µm), respectively. Moreover, the appearance of the luminal epithelial cells and endometrium for the BTE +

Table 1: Effect of herbal teas on the diameters of uterine layersamong mice groups

	Endometrium thickness (µm)	Myometrium thickness (µm)	Perimetrium thickness (µm)	Luminal epithelial cells height (µm)
RTE + BPA Group	230.11±4.93^{c}	247.13±4.58^{b}	12.59±0.25^{c}	17.02±0.14^{c}
GTE + BPA Group	223.53±0.48^{e}	233.95±3.61^{c}	12.99±0.54^{c}	18.15±1.22^{a}
BTE + BPA Group	244.11±3.33^{b}	245.97±2.63^{b}	14.55±0.17^{b}	18.57±0.28^{b}
Group (+)	180.91±2.94^{d}	255.1±3.12^{a}	10.13±0.73^{d}	8.77±0.34^{d}
Group (-)	261.11±1.44^{a}	256.17±2.61^{a}	19.58±0.18^{a}	19.33±0.57^{b}

*Each value presents as mean ± standard deviation. (n=3), Mean with different superscripts on the same column are significantly different ($p < 0.05$).

BPA group was close to normal. This indicated that the blue and red tea extracts might prevent negative changes in BPA-exposed mice. The results were in agreement with the previous findings by Markey *et al.* (2005).

DISCUSSION

It is commonly known that BPA is an endocrine disruptor which can mimic the effects of natural oestrogen, cause metabolic imbalances and develop illnesses (Newbold *et al.,* 2007). Prolonged exposure can result in irreversible infertility. In several animal models, exposure to BPA reduces fertility, messes with the estrous cycle, reduces the primordial follicle pool, and interferes with steroidogenesis (Ziv-Gal *et al.,* 2013). The findings on uterine weight were consistent with earlier research (Rodríguez *et al.,* 2010). Several factors can influence offspring weights as mice strains, age and the time of BPA exposure (Mendoza-Rodríguez *et al.,* 2011). The dietary intake of carotenoids in the diet can increase the production of male offspring than the females (McGraw *et al.,* 2005). This indicated that the blue tea extract might be employed as a treatment after BPA toxicity exposure and is safe for oral intake due to the presence of antioxidants. BPA is a xeno-estrogen that may lead to lipid peroxidation, all of which may cause organ diseases (Markey *et al.,* 2005). Moreover, epidemiological research revealed that infertile women had elevated levels of ROS (Polaka *et al.,* 2001). MDA can function as a co-carcinogen, inhibit protective enzymes, and cause hepatotoxicity (Bauer, 2000). According to a prior study (Patisaul *et al.,* 2012), the reduction levels of oxytocin in plasma were the reason why the adolescent animal model exposed to BPA toxics showed increased levels of anxiety. The hormone oxytocin aids in relaxation and lowers cortisol and blood pressure (Bhutada *et al.,* 2010). According to a study by Cheng and Li (2012), antioxidant components have been shown to inhibit the release of cortisol and corticotropin-releasing hormones under continuous stress. Bosquiazzo *et al.* (2013) reported the appearance of some deformities as persistent anoestrus which appeared in old animals undergoing reproductive senescence after exposure to BPA toxics.

CONCLUSION

BPA exposure negatively affects murine reproduction, but herbal teas have a protective effect, enhancing it. This study investigated the potential benefits of three types of herbal teas: blue tea (*Clitoria ternatea*), red and green tea (*Camellia sinensis assamica*). All treatment groups showed improvements in uterine structure and weight; increased offspring weights and improved reproductive biomarkers, including plasma levels of MDA, oxytocin, and cortisol. The impact on other reproductive hormones and the specific mechanisms of BPA damage to other organs require further research.

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