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Effect of mangosteen peel extract on BPA-exposed murine during gestation

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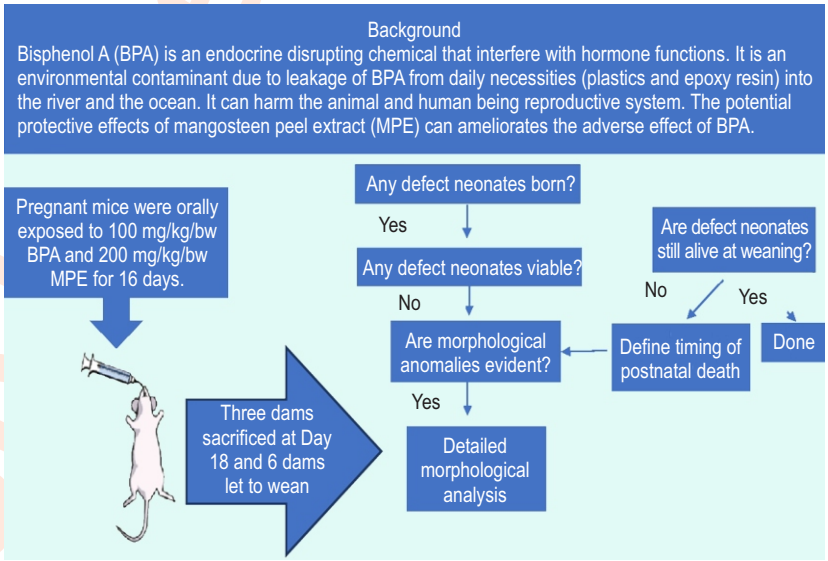
Abstract

Aim: To evaluate the potential protective effects of mangosteen peel extract against BPA-induced abnormalities on-pregnant mice fetus at implantation stage and offspring at post-parturition.

Methodology: Pregnant mice were orally administered with BPA (100mg kg^{-1} b.wt.) and mangosteen peel extract (200mg kg^{-1} b.wt.) for 16 days. In order to evaluate the effect of MPE treatment on fetus at implantation stage, the pregnant mice were euthanized at day 18 and the fetus number and morphology were examined. Another group of treated dams, were allowed to undergo parturition for evaluating the of maternal weight, litter size and offspring sex-skewness.



Results: Upon feeding Mangosteen peel extract (MPE), the average daily weight gain of dams were not significantly different from the control and BPA treated dams. The fetus derived from BPA treated dams were detected with abnormalities such as under development, haemorrhage and absence of vein, whereas fetus from dam treated with MPE and BPA as well as control were normal. The average litter size of all the treatment groups were not significantly different from the control group. BPA treated mice had lower pups survival up to 6 weeks compared to the groups treated with MPE and control. Test of proportion analysis showed BPA-treated group had significantly higher fraction female ratio.

Interpretation: BPA is known as endocrine disruptor causing oxidative stress to female reproductive system, hence mangosteen peel extract contains antioxidant substances that have the potential to ameliorate the adverse effects of BPA exposure on dams during pregnancy and its fetus development.

Key words: Bisphenol A, Endocrine disruptor, Fertility, Mangosteen peel extract

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Introduction

Endocrine-disrupting chemicals are compounds that mimic, block or interfere with the function of hormones in the body's endocrine system (Schug *et al.,* 2011). Bisphenol A (BPA) is one among them which serve as plasticizer in the production of polycarbonate plastics, epoxy resin and unsaturated polystyrene. The usage of BPA has progressively increased worldwide due to its extensive applications in manufacturing of daily necessities such as plastic bottles, food packaging, thermal paper, electronic equipment and medical appliances (Vandenberg *et al.,* 2007). Humans can be exposed to BPA via ingestion, inhalation and skin contact at micrograms per kg of body weight daily. BPA has demonstrated multiple adverse effects on laboratory animals, in term of neurological development, behavioral changes, reproduction and lead to carcinogenesis (Inadera, 2015). Earlier, studies have revealed the multiple adverse effects of BPA, as an endocrine disruptor, on the reproductive system. In males, the effects of BPA include decreased sperm motility, impaired spermatogenesis and decreased fertility of male offsprings. In females, the BPA targets the reproductive organs, mammary gland, ovary, oviduct, uterus and placenta (Vandenberg *et al.,* 2007). BPA causes uterine endocrine disruptions, oxidative stress and inflammation in the reproductive tract of female mice at sub-chronic dosage (Signorile *et al.,* 2010).

Research has shown that oxidative stress with the elevation of reactive oxygen species in the body is harmful and the presence of antioxidants are important to counteract the reactive oxygen species in the body (Wang *et al.,* 2017). Escalation of ROS can induce pathological consequences in oocyte maturation, ovulation, fertilization, implantation, and embryo development, which can ultimately influence the outcome of pregnancy (Wang *et al.,* 2017). Previous studies have reported that antioxidants play significant role in treating reproductive disease and infertility by controlling oxidative stress (Agarwal *et al.,* 2012; Liu *et al.,* 2018; Tahmasebi *et al.,* 2018; Wang *et al.,* 2017). Antioxidant substances especially quercetin, catechin and anthocyanins have been proven its potential to ameliorate polycystic ovary syndromes (PCOS) and prevent ovarian aging due to their antioxidant effects on ROS pathways by either inhibiting NF-κB pathway or by increasing antioxidase activities and their gene expression (Liu *et al*., 2018; Tahmasebi *et al*., 2018).Current research trends are being focused on exploring natural plant-based source of antioxidants to counter the effects of oxidative stress. The mangosteen peel extract (MPE) is an industrial waste but contain natural antioxidants such as phenolic acids and flavonoids, which possess biological and medicinal properties, especially antioxidant properties (Suttirak and Manurakchinakorn, 2014). There are some similar studies like tualang honey with high total phenolic compounds and flavonoids showed protective effects against BPA-induced toxicity in female rats (Mohamad Zaid *et al*., 2015). Tahmesiet al., 2018 study also proven that antioxidant effects of calligonuum extract is able to decrease oxidative stress in mouse model and significantly decrease PCO which is a common reason of infertility (Tahmasebi *et al*., 2018). In view of the above, this study was conducted to evaluate the potential protective effects of mangosteen peel extract against BPA-induced abnormalities on-pregnant mice fetus at implantation stage and offspring at post-parturition.

Materials and Methods

Experimental design: 40 adult ICR female mice weighing 27±3g were used in this study. The animals were housed in polypropylene cages under standard hygienic condition and fed with rodent chow and water ad libitum in a temperature-controlled room (22°C) with a 12-hr light, 12-hr dark cycle. Animals were acclimatized for one week to the experimental animal room conditions and in order to optimize treatment doses, all animals were fasted for 1 hr prior to treatment.

Animals were randomly assigned into four groups (n=10 per group) *viz.* Vehicle group: administered orally 0.2 ml of olive oil; MPE group: animals orally gavaged with mangosteen peel extract dissolved in water at the dose of 200 mg kg^{-1} daily; BPA group: animals orally gavaged with bisphenol A dissolved in olive oil (as vehicle) at the dose of 100mg kg^{-1} daily; MPE + BPA group: animals orally gavaged with MPE concurrently with BPA. The dams were treated for 16 days consecutively according to the treatment assigned. All animal handling and experiments were conducted as per the guidelines set by the National Institute of Health (Guide for the Care and Use of Laboratory Animals) which were approved by the Scientific and Ethical Review Committee, Universiti Tunku Abdul Rahman (Approval number: U/SERC/ 54/ 2019).

Macroscopic analysis: Macroscopic analysis was conducted on fetus at implantation stage and offspring at post-parturition stage. Implantation stage is the stage before the pregnant mice gives birth to pups. During implantation stage, maternal weight was recorded until gestation day (GD) 18 to determine the effect of treatments on the body weight. First batch of treated mice (n=4) were euthanized at GD18 of gestation. The presence of resorption or abnormalities on implantation site of the uterus, number of fetus, wet weight and crown rump length of fetus were recorded. Another group of treated mice (n=6) were allowed to undergo parturition. The gestation period of dam, litter size, sex skewness of pups, survival rate and weight of the pups were examined and recorded for further analysis.

Chemicals: Bisphenol A ($C_{15}H_{16}O_2$) with purity 99% and all the chemical were purchased from Sigma Chemical Co. (St.Louis, MO, USA). MPE powder were obtained from Furley Sdn. Bhd., Pahang, Malaysia.

Statistical analyses: SPSS (ver.23) was used for computation of data. Results obtained from the experiment were presented as mean with standard deviation and were analyzed using One-way analysis of variance (ANOVA) and Tukey-Kramer Post-hoc test to evaluate the significance between the data. Sex ratio (fraction female pups) for all the treatment groups was tested against the

expected value of 0.5 by using Test of Proportion (Rosenfeld *et al.,* 2003). The -95%confidence level was used to evaluate the difference between treatment groups, $p<0.05$ is considered as statistically significant.

Results and Discussion

Bisphenol A is a well known endocrine disrupting compound which possess weak estrogenic properties (Ribeiro *et al.,* 2017; Vandenberg *et al.,* 2009). It is used mainly in plasticizer. (Matuszczak *et al.,* 2019; Signorile *et al.,* 2010; Vandenberg *et al.,* 2007). In a non-monotonic dose-response study, both high and low doses of Bisphenol A exhibit oxidative stress and induced reactive oxygen species (ROS) that can damage cellular macromolecules (Gassman, 2017). The negative effect of ROS and lipid peroxidation are counteracted by antioxidant defense system. Mangosteen peel has detectable role in almost all biochemical reactions and possess vital antioxidants property that protect tissues from oxidative stress attributable to their safety dietary administration in large concentration (Jaisupa *et al.,* 2018; Suttirak and Manurakchinakorn, 2014). Sunarjo *et al.* (2017) reported that extract of mangosteen skin with dosage ≤ 5000 mg kg^{-1} b.wt. is non toxic and safe for consumption.

In this study, all treatment groups exhibited gain in body weight that was comparable with the control group (Fig. 1). This observation could be due to the non-monotonic dose-response of BPA. BPA only affects the maternal body weight in low dose which is US EPA reference dose of 50 µg kg^{-1} day^{-1} or the LOAEL of 50 mg kg^{-1} day^{-1}. However, in this study the dose of BPA was 100 mg kg^{-1} day^{-1}. The non-monotonic dose-response ofBPAwere also reported by some studies (Vandenberg, 2013; Vandenberg *et al.,* 2009). The results for average implantation site, fetus weight, uterus weight and crown rump length are presented in Table 1. The average fetus weight for control, BPA, MPE and MPE+BPA group were 0.85 g, 0.92 g, 0.84 g and 0.93 g, respectively. The average number of implantation site were not significantly different but arguably higher in BPA treated mice (13.3) compared to the control (11.7). The number of implantation sites for MPE+BPA and MPE were 12.0 and 12.0, respectively. The uterus weight of dams was not significantly different ($p<0.05$) for all control, BPA, MPE and MPE+BPA group with 14.39 ± 1.67 mg, 18.11 ± 1.59 mg, 16.62 ± 1.97mg, 16.39 ± 1.48 mg respectively (Table 1). The average crown rump length of the fetus derived from dams across all treatment groups were not significantly different ($p<0.05$) but numerically higher in BPA (1.89 cm), MPE+BPA (1.94 cm) and MPE (1.81 cm) group, respectively, compared with control (1.65 cm). BPA treated mice showed defects in some of their fetus. One or two of the fetuses from each BPA treated dam were observed with haemorrhage, reduced size or no blood vein (Fig. 2).

Pregnant mice exposed to BPA shows BPA-related embryopathy and malformations (Müller *et al.,* 2018). Evidence of fetus morphological and functional teratogenicity after BPA exposure. The has been reported affected feotus were typically premature and/or with stunted growth (Burstyn *et al.,* 2013; Lee *et al.,* 2008). Similarly, in this study fetus showed stunted growth and haemorrhage feature after in utero exposure to BPA (Fig. 2). The MPE+BPA group fetus, however, did not show any morphological abnormalities, thereby, confirming the potential of mangosteen peel extract in ameliorating the adverse effects of BPA. However, interestingly crown rump length (CRL) and the body weight of the fetus of BPA treated mice arguably was higher compared to the

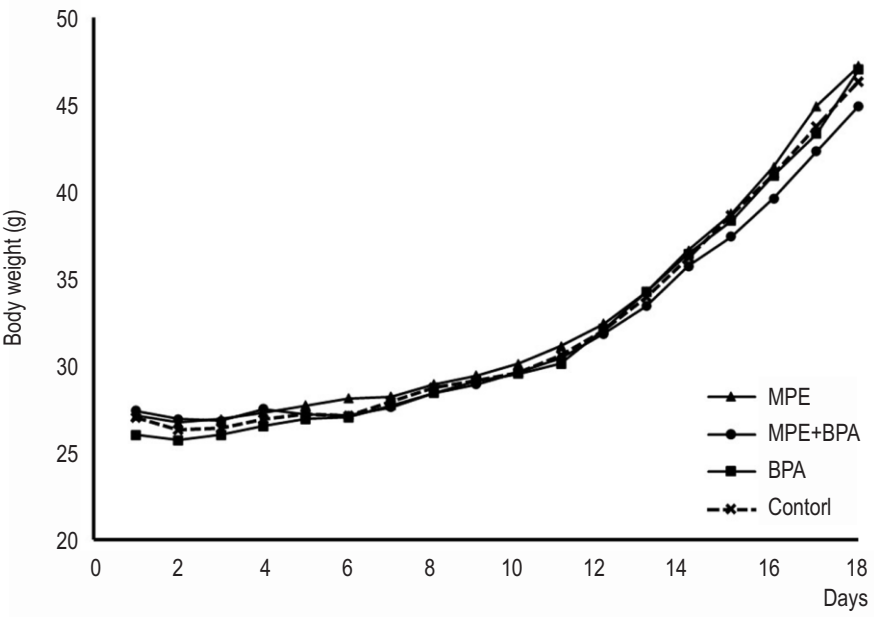

Fig. 1: Body weight gain in maternal ICR mice administered with BPA, MPE, MPE+BPA and Olive Oil (vehicle control) during gestation days (GD) 1 to 18.

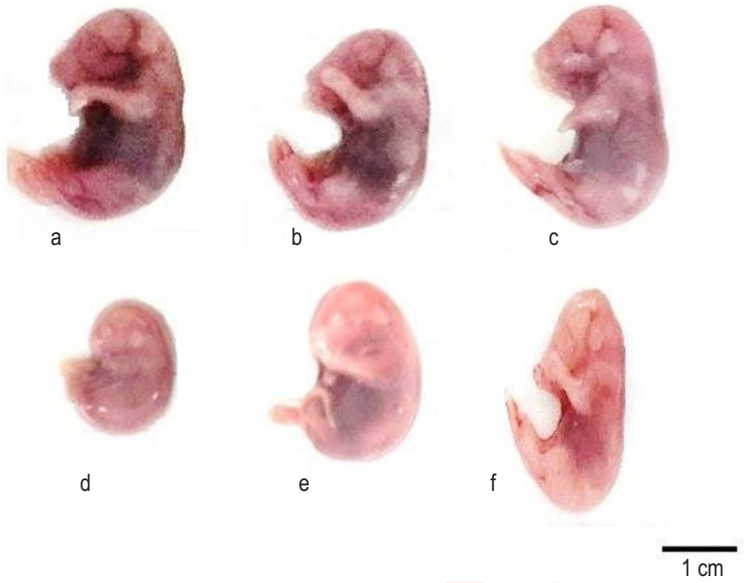

Fig. 2: Fetus from 18-days-old ICR mice exposed in utero (a)-(c)Normal fetus from vehicle control, MPE and MPE+BPA, (d) Growth stunted fetus from BPA (e) Haemorrhage fetus from BPA and (f) No blood vein fetus from BPA.

Table 1: Fetus condition, implantation site and uterus weight of treated dams from different treatment groups

Parameters	Vehicle control	BPA	MPE+BPA	MPE
Average fetus weight, (g)	0.85 ± 0.14	0.92 ± 0.11	0.93 ± 0.07	0.84 ± 0.19
Implantation site (s)	11.70 ± 0.60	13.30 ± 1.20	12.00 ± 1.00	12.00 ± 1.70
Uterus weight, (mg)	14.39 ± 1.67	18.11 ± 1.59	16.62 ± 1.97	16.39 ± 1.48
Crown-rump length, (cm)	1.65 ± 0.16	1.89 ± 0.19	1.94 ± 0.72	1.81 ± 0.16

Mean±SD

Table 2: ANOVA, Skewness and kurtosis tests for post-parturition data

Parameters	Control	BPA	MPE+BPA	MPE
Gestation period (days)	20.0±0.0	19.8±0.8	20.0±0.0	19.8±0.4
Average litter size	10.7±1.0	10.7±1.0	10.0±1.3	11.3±1.0
Litter size (pups), n	64	64	60	68
Survival rate (%)	100.0±0	82.8±7.4[a]	96.7±5.2	98.7±3.1
Fraction female pups	0.47	0.60[b]	0.47	0.51

Mean±SD; n=total number of mouse offspring; [a]p<0.05 vs. vehicle control, BPA and MPE (Tukey's multiple regression test); [b]p<0.05 vs 0.5 sex ratio deviated significantly from 0.5 (Test of proportion)

controls and MPE treated group. This result can be relatable to a review which stated that endocrine disrupting compounds can contribute to adult obesity starting from foetal development stage by influencing adipocytes mechanism (Vom Saal *et al.,* 2012).

A study by Nikaido *et al.* (2004) also reported increased in the body weight in the female offspring of CD-1 dams treated with 0.5 or 10 mg BPA kg^{-1} b.wt. day^{-1} on days 15–18 of gestation (Nikaido *et al.,* 2004). Due to these reported cases of increased body weight and size, some possible mechanism of BPA actions was proposed. Somehow, adiposity and glucose mechanisms were involved. A study reported the importance of dose and timing of exposure to xenoestrogens and estrogenic compound itself in determining their effects on adiposity and glucose homeostasis (Tudurí *et al.,* 2018). Studies also suggest that BPA affects preadipocytes. Micromolar concentration of BPA enhance adipocyte differentiation and lipid accumulation in target cells (Masuno *et al.,* 2002; Wada *et al.,* 2007). In addition, BPA also

enhanced basal glucose uptake due to increased GLUT 4 protein (Sakurai *et al.,* 2004). These reported actions of BPA that resulted in increase of adiposity, body weight and size of fetus BPA treated mice fetus had a higher body weight and crown-rump length. *In utero* exposure of adult female mice to BPA was previously shown as teratogenic (Ziv-Gal *et al.,* 2015). The results of this study revealed that *in utero* administration of BPA to pregnant murine model showed adverse effect on the fetus. At dose level of 100 mg kg^{-1} BPA had statistically significant effects on the offspring compared to control, MPE and MPE+BPA treated groups. This showed that 200 mg kg^{-1} MPE was able to ameliorate the BPA adverse effects. The effects observed were the survival rate and the sex fraction of the offspring. The proportion of pups born alive and surviving to weaning was significantly affected by exposure to BPA. The BPA-derived pup survival rate was only 87% compared to controls (100%), MPE+BPA (97%) and MPE (99%) groups (Table 2).This showed mangosteen peel extract is able to counteract the negative impact of BPA during fetal developmental stage. This observation could be due to the presence of antioxidants in MPE which is in agreement with the findings by Mohamad Zaid *et al.,* 2015 that showed the protective effect of tualang honey on uterine is due to the antioxidant compounds. Changes in uterine morphology could be the direct action of BPA on the DNA that results in alteration of gene expression during fetal development (Mohamad Zaid *et al.,* 2015). The gestation length was not significantly different across all the treatment groups. For the control, BPA, MPE+BPA and MPE, the average gestation lengths were 20.0 ± 0.0, 19.8 ± 0.8, 20.0 ± 0.0, 19.8 ± 0.4 days respectively (Table 2). The number of pups in all the treatment groups were not significantly different from the controls. The litter size for control, BPA, MB and MPE group were 64, 64, 60 and 68 respectively and the averages of the litter size were 10.7 ± 1.0, 10.7 ± 1.0, 10.0 ± 1.3, 11.3 ± 1.0 respectively (Table 2).

Survival rate was measured by the number of offsprings that were able to survive until maturation *i.e.,* 42 days. The survival rate of *in utero* exposure of BPA is significantly different compared to the other treatments. As compared to other treatment groups the lowest survival rate (82.8%) of pups was found in BPA treated groups (Table 2). The fraction male pups derived from dams treated with control, BPA, MPE+BPA and MPE was 0.47, 0.6, 0.46, 0.51, respectively. Test of proportion analysis were performed to test the normal distribution of results against the expected value 0.5. The results showed that BPA treated group deviated significantly from 0.5. Moreover, in utero BPA exposure significantly increased the fraction female ratio (Table 2). This result can be due to the direct effect of BPA on the fetus or due to fetal exposure to an altered maternal metabolism (Alonso-Magdalena *et al.,* 2010). This female bias sex ratio result is in confirmation with the reports of Chen *et al.* (2015) and Vo *et al.* (2015). Chen *et al.* (2015) exposed zebrafish with chronically 1nM BPA which resulted in significantly altered female-biased sex ratio. Genetic sex in most animals is determined at the time of fertilization. However, even when X chromosome-bearing oocyte receives a Y chromosome from the sperm, the sex is still undetermined because sex differentiation does not start until 11.5 days post coitum when male-determining gene Sry is expressed.

The expression of Sry induces a complex network of testis-specific gene expression, regulation and interaction that directs differentiation of genital ridge into a testis. If expression of Sry gene does not occur, or its expression is delayed, female-determining gene pathways are activated, molecular cascades and cellular events drive the genital ridges towards ovary development (Wilhelm *et al.,* 2007). Therefore, BPA exposure during gestation period did suppressed or delayed the expression of Sry gene and activated the female-determining pathways resulting in more female offsprings than male offspring. However, in this study, the treatment with MPE significantly attenuated the BPA deviations in sex alteration, which could be due to the antioxidant effects of MPE which reduced in the number of free radicals caused by the BPA. As MPE was reported as an effective antioxidant in scavenging free radicals (Suttirak and Manurakchinakorn, 2014; Widowati *et al.,* 2020). Furthermore, the experimental data in this study showed that in utero treatment of BPA does not affect the maternal generation in terms of body weight, gestation period and litter size. However, the BPA adverse effects seem to be exerted prominently on the next generation than the treated dam itself.

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Add-on Information

Authors' contribution: K.L. Loh: Carried out the animal feeding, data collection, macroscopic analysis, statistical analysis and drafted the manuscript; **P.J. Kwong:** Participated in experimental design and drafted the manuscript; **M.Y. Chan:** participated in experimental design; **G.C. Tan:** Participated in experimental design and drafted the manuscript.

Research content: The research content of manuscript is original and has not been published elsewhere.

Ethical approval: Ethics approval approved by UTAR Science and Ethical Review Committee (U/SERC/54/2019).

Conflict of interest: Loh Khai Lun declares that he has no conflict of interest.

Data from other sources: Not applicable.

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