UNIVERSITI TEKNOLOGI MARA

PROCYANIDIN C-1 INTERVENTION ON BISPHENOL A- INDUCED REPRODUCTIVE DYSFUNCTION IN MALE MICE

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ABSTRACT

Exposure to bisphenol A (BPA), an endocrine-disrupting chemical, is known to result in reproductive dysfunction. Procyanidin C-1 (PCY-1), derived from grape seed extract, is a potent antioxidant with antiviral, antimelanogenic, and immunostimulatory properties. This study determined the effect of PCY-1 intervention in mitigating the adverse effect of BPA on sperm parameters, testicular morphology, serum levels of testosterone, oestradiol and LH, and the testicular expression of genes related to apoptosis (*Bax* and *Bcl-2*), mitochondria (*Mfn1* and *Opa1*) and oxidative stress (*Sod1* and *Gpx1*) in C57BL/6NTac mature adult and aged mice. The mice were divided into four groups: control group (H2O), BPA-induced group (BPA), PCY-1-only treatment (PCY-1) and co-administration of PCY-1 and BPA (PCY-1+BPA). The dose for BPA is 15 mg/kg body weight, and the dose for PCY-1 is 20 µg/kg body weight. The treatments were administered daily via oral gavage for a duration of 35 days. Intervention of PCY-1 in BPA-induced mature adult mice exhibited body weight loss and significant increases in the testes coefficient. PCY-1 intervention also showed increase on sperm concentration and a significant decrease on abnormal sperm morphology in BPA-induced mature adult mice. Histological examination of testes also showed a significant enhancement of the diameter of seminiferous tubules in the PCY-1 intervention BPA-induced mature adult mice. The PCY-1 intervention had significant effects on testosterone and LH levels, leading to a decrease, while oestradiol levels increased in mature adult mice. The PCY-1 intervention in BPA-induced mature adult mice decreased *Bax* gene expression and increased *Bcl-2* gene expression. The PCY-1 intervention also downregulated *Mfn1*, *Opa1* and *Sod1* gene expression. In the BPA-induced aged mice, PCY-1 intervention significantly increased body weight and seminal vesicle coefficient. The intervention of PCY-1 in BPA-induced aged mice also revealed an improved testicular and sperm parameter with a lower percentage of abnormal sperms and greater seminiferous tubules width and epithelial height. In term of the hormonal analysis, only a significant reduction in oestradiol levels was observed in the intervention of PCY-1 in BPA-induced aged mice. In addition, no significant results were obtained from the measurement of antioxidant levels in the BPA-induced aged mice with PCY-1 intervention. The intervention of PCY-1 in BPA-induced aged mice also showed a decrease in the *Bax* gene expression and an increase in the *Bcl-2* gene expression, while the *Mfn1, Opa1, Sod1* and *Gpx1* genes showed a significant upregulation. In conclusion, PCY-1 was able to attenuate the negative effects of BPA on the reproductive parameters of mature adult and aged mice, possibly via anti-apoptotic mechanisms. The hypothesis that PCY-1 protects the mature and ageing male reproductive system from the harmful effects of BPA is therefore accepted.

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CHAPTER 1
INTRODUCTION

1.1 Background of study

The total fertility rate (TFR) represents the average number of children that a woman would have if she were to have the same fertility rates at every stage throughout her childbearing years. If there is no net migration and mortality rates remain constant, a total fertility rate of 2.1 children per woman guarantees overall population stability, often known as the "replacement rate" (Organisation for Economic Co-operation and Development, 2019). The global TFR has steadily declined over the last 50 years, especially in the more developed countries. It is estimated that the TFR will be 2.3 births per woman worldwide in 2023 (United Nation Population Fund, 2022). Southeast Asia has also seen a rapid decline in fertility rates from 5.267 in 1970 to 1.82 in 2019. Brunei, Thailand, Singapore, Malaysia, and Vietnam are among the ASEAN countries with total fertility rates below the replacement levels. Timor-Leste has the highest fertility rate among Southeast Asian countries with 3.1 children per woman in 2021, while Singapore has the lowest fertility rate with 1.1 children per woman (World Bank, 2022).

Numerous factors contributed to the decline in TFR, including the increasing availability of modern contraceptives, especially sterilisation, and the legalisation of induced abortion, a marked increase in deferred parenthood, and a decline in fertility among married couples (Gubhaju & Moriki-Durand, 2003). Infertility currently affects about 48 million couples and 186 million individuals worldwide (World Health Organization, 2021b). The prevalence of infertility among couples of reproductive-age ranges from 12.6% to 17.5%, with higher rates in certain regions such as the Americas, Western Pacific, Africa and Europe (Cox et al., 2022).

About half of all cases of infertility are due to male factors, that include exposure to chemicals/toxins, ageing, hormonal imbalances, chromosomal abnormalities, physiological abnormalities, lifestyle problems and others (Anawalt & Page, 2021; Moreira et al., 2021; Babakhanzadeh et al., 2020; Mazur & Lipshultz, 2018). Endocrine disrupting chemicals (EDCs) are exogenous chemical compounds that can disrupt the endocrine system and have various adverse health effects by affecting different organs and systems in the human body. Global contamination is the result of industrialisation