



## Protocatechuic acid modulates reproductive dysfunction linked to furan exposure in rats

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### ABSTRACT

The reproductive toxicity associated with furan exposure in both animals and humans has been documented. Protocatechuic acid (PCA), a dietary polyphenolic chemical, reportedly elicits beneficial effects on the male reproductive system. However, the influence of PCA on the reproductive toxicity related to furan exposure is unavailable in the literature. The current study evaluated the effects of PCA on the dysfunctional reproductive axis caused by furan exposure in rats. Experimental animals were exposed to furan (8 mg/kg) or co-treated with furan (8 mg/kg) and PCA (25 or 50 mg/kg) for twenty-eight successive days. Results revealed that PCA treatment significantly alleviated furan-mediated declines in sperm production and characteristic qualities as well as in serum levels of prolactin, luteinizing hormone, follicle-stimulating hormone, and testosterone. Further, PCA attenuated furan-induced reduction in antioxidant enzyme activities and testicular function marker enzymes, namely lactate dehydrogenase, glucose-6-phosphate dehydrogenase, acid phosphatase, and alkaline phosphatase. PCA effectively mitigated furan-mediated increases in myeloperoxidase activity, levels of reactive oxygen and nitrogen species, nitric oxide, tumour necrosis factor- $\alpha$ , and interleukin-1 $\beta$  in testes, epididymis, and hypothalamus of rats. Moreover, PCA increased anti-inflammatory cytokine interleukin-10 but suppressed caspase-9 and caspase-3 activities and ameliorated injuries in the testes, epididymis, and hypothalamus of furan-treated rats. In conclusion, PCA ameliorated deficits in the hypothalamic-pituitary-gonadal axis function in furan-exposed rats by suppressing oxido-inflammatory stress and apoptosis.

### 1. Introduction

Furan (C<sub>4</sub>H<sub>4</sub>O) is a volatile heterocyclic compound unintentionally produced during the thermal processing of food (Authority, 2009; Morehouse et al., 2008; Moro et al., 2012). Furan and furan analogs are reportedly formed from the interaction of specific naturally occurring molecules such as ascorbic acid and carbohydrates with some amino acids via a process involving the Maillard reaction (Becalski and Seaman, 2005; Bolger et al., 2009; Limacher et al., 2007; Yaylayan, 2006). Previous investigations revealed the presence of furans in commonly consumed foods, including brewed coffee, fried cereal products, hydrolyzed soy protein, canned and jarred foods, baby food, and infant formulas (Karacaoglu and Selmanoglu, 2010; Morehouse et al., 2008). Furthermore, report by the European Food Safety Authority (EFSA) indicated that the primary sources of furan exposure to children are milk-based products, fruit juices, and cereal-based products. At the

same time, adults are primarily exposed to furans, via brewed coffee (Authority, 2011). Furan concentrations in coffee ranges from whole 4.6 mg/kg in roasted coffee beans to 2.4 mg/kg in ground roasted coffee, while composite foods (vegetable-based, cereal-based, and prepared salads) ranges from 20 to 57  $\mu$ g/kg (Chain et al., 2017).

Moreover, furan and furan analogs are environmental contaminants because they are the primary component of wood and cigarette smoke (Environment and Climate Change Canada, 2018; Feng et al., 2011; Tabaran et al., 2019). Furan is a synthetic intermediate in the manufacturing of pesticides, pharmaceuticals, and stabilizers (Cancer, 1995). Consequently, furan has been detected in industrial effluents, surface water, haze, and acid hydrolysates (Gill et al., 2010). Epidemiological studies demonstrated the occurrence of furans in the placenta and milk of humans (Leino et al., 2013; Li et al., 2009). The semen of infertile males reportedly contained high levels of furans compared with fertile males, which signifies an association between furan exposure and

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