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Caspase-3 activities and androgen receptor expression in rats' testis during the early biochemical and histopathological changes induced by a carcinogen, Diethylnitrosamine: role of probiotics and pyridazine derivatives

Ahmed A. Morsi¹, Sahar B. Ahmed², Neveen M. Saleh³, Rania A.H. Abd El-Aal⁴, Tamer El Malah⁵ and Asmaa M. Elsayed¹

¹Department of Histology and Cell Biology, Faculty of Medicine, Fayoum University, Fayoum, Egypt, ²Division of Biochemistry, ³Microbiology Department, ⁴Developmental Pharmacology Department, National Organization for Drug Control and Research (NODCAR), Giza, Egypt, ⁵Photochemistry Department, Chemical Industries Research Division, National Research Centre, Cairo, Egypt

Background: Diethylnitrosamine (DENA) is a common environmental toxicant with a well-known hepatocarcinogenic potential. **Aim:** The current study aimed to: 1) investigate the carcinogenic toxicity of DENA on the rats' testis, 2) to elucidate the role of caspase-3 activities and androgen receptors (AR) in this toxicity, and 3) to assess the effect of treatment with *Lactobacillus casei* (LAB) and 3-methylsulfanyl-4,6-diphenyl-pyridazine (MDP) on testicular tumorigenesis. **Material and Methods:** Sixty Sprague–Dawley albino rats were divided into 6 groups; control, DENA-alone, DENA+MDP, DENA+LAB, DENA+DOX (Doxorubicin) and DENA+DOX+MDP. In all experimental animals, DENA was injected intraperitoneal (i.p) (55 mg/kg) twice weekly for 6 weeks. MDP (10 mg/kg, ip), LAB (1.5 x 10⁹ CFU/kg, oral) and DOX (10 mg/kg, ip) were administered twice weekly for the following 4 weeks. Serum testosterone, anti-mullerian hormone, alpha-fetoprotein, tumor necrosis factor, nitric oxide, glutathione peroxidase, and sperm analysis were determined. Histopathological evaluation of the testis was done. AR and caspase-3 activities were detected by immunohistochemistry. **Result:** The DENA-alone-treated animals showed disturbed biochemical assays and marked tubular degenerative changes, in addition to notable Leydig cell hyperplasia (LCH) in the histological findings. MDP, LAB, DOX reversed the biochemical changes with less extent in DOX treatment. No further improvement was noted in the tubular histoarchitecture in DOX-treated groups meanwhile, LAB treatment restored LCH with a partial effect in MDP treatment. **Conclusion:** DENA induced AR-immunopositive Leydig cell hyperplastic changes, in addition to spermatogenic cytotoxicity with increased tubular caspase-3 activities. LAB and MDP reversed biochemical changes and had a curative potential on the testis with a partial anti-proliferative effect for MDP.

Keywords: Androgen receptors, Caspase-3, Diethylnitrosamine, *Lactobacillus casei*, 3-Methylsulfanyl-4,6-diphenyl-pyridazine, Pyridazine derivatives, Testis