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Title: Role of Ferroptosis in Tamoxifen-induced Reproductive Impairments in Mature Male Rats

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Tamoxifen (TMX) as a selective estrogen receptor modulator is widely used for the treatment of hormone-dependent breast cancer in males and females. The aim of this study was to elucidate the role of ferroptosis in TMX-induced reproductive impairments in mature male rats. Twenty-four adult male Wistar rats were categorized into four equal groups including control (0.10 mL olive oil; orally (PO), daily for 10 days), TMX_{200} (200 µg k^{-1} TMX; PO, daily for 10 days), TMX_{400} (400 µg k^{-1} TMX; PO, daily for 10 days) and TMX_{800} (800 µg k^{-1} TMX; PO, daily for 10 days). All animals were euthanized after 35 days and testicular oxidant/anti-oxidant status, lipid peroxidation (LPO) level, glutathione peroxidase (GPx) activity, GPx4 and SLC7A11 expressions and histopathological alterations as well as epididymal sperms characteristics were analyzed. The TMX administration led to significant dose-dependent reductions in testicular GPx activity and GPx4 and SLC7A11 mRNA levels and epididymal sperms quantity and quality along with increases in testicular LPO and oxidative stress index levels and marked histopathological alterations in testicular tissue. Taken together, these findings introduce ferroptosis as a novel mechanism of TMX-induced male reproductive toxicity in rats.

Keywords: Ferroptosis, Rat, Sperm, Tamoxifen, Testis