

## **Eighth research**

### **Title**

Pirfenidone targeted mechanisms for alleviating methotrexate- induced testiculopathy in Wistar rats.

**Naunyn-Schmiedeberg's Archives of Pharmacology (2024)**

### **ABSTRACT:**

Testicular injury and affected spermatogenesis are major complications of methotrexate (MTX) use. Oxidative stress is one contributing process leading to inflammation and apoptosis induction. Pirfenidone (PFD) is a well-known anti-fibrotic drug prescribed for interstitial lung fibrosis, in addition to anti-inflammatory, antioxidative, and antiapoptotic capabilities. The study aimed to explore the potential protection afforded by PFD in a rat model of MTX-induced testiculopathy. The experimental design included four groups, each containing seven adult Wistar rats: control, PFD (500 mg/kg/day, orally)-, MTX (0.5 mg/kg, intraperitoneal, twice weekly)-, and PFD/MTX-treated groups. Treatment continued for 4 weeks. Blood and testicular samples were harvested for biochemical, histological, immunohistochemical, and polymerase chain reaction (PCR) analyses. Also, the testicular damage and spermatogenic activity were graded by the testicular injury and Johnsen scoring system, respectively. PFD positively affected the serum testosterone (TST) level, reduced the testicular inflammatory mediators [tumor necrosis factor-  $\alpha$  (TNF- $\alpha$ ), interleukin-  $1\beta$  (IL-  $1\beta$ )], reduced the testicular oxidative burden, increased superoxide dismutase (SOD), and protected the testicular histological structure. In addition, antifibrotic effects, anti-caspase 3, and PCNA enhancement activity were recorded. PFD exhibited a protective potential and mitigated the MTX-induced testiculopathy via suppression of testicular oxidative stress, inflammation, fibrosis, and apoptosis and

retaining the testicular proliferative efficacy as confirmed by histological, immunohistochemical, and biochemical methods.

**Keywords:** Methotrexate gonadotoxicity · Oxidative stress · Apoptosis · Pirfenidone · Rat testicles.