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Molecular insights into the renal and hepatic toxicity of the fungicide Trifloxystrobin

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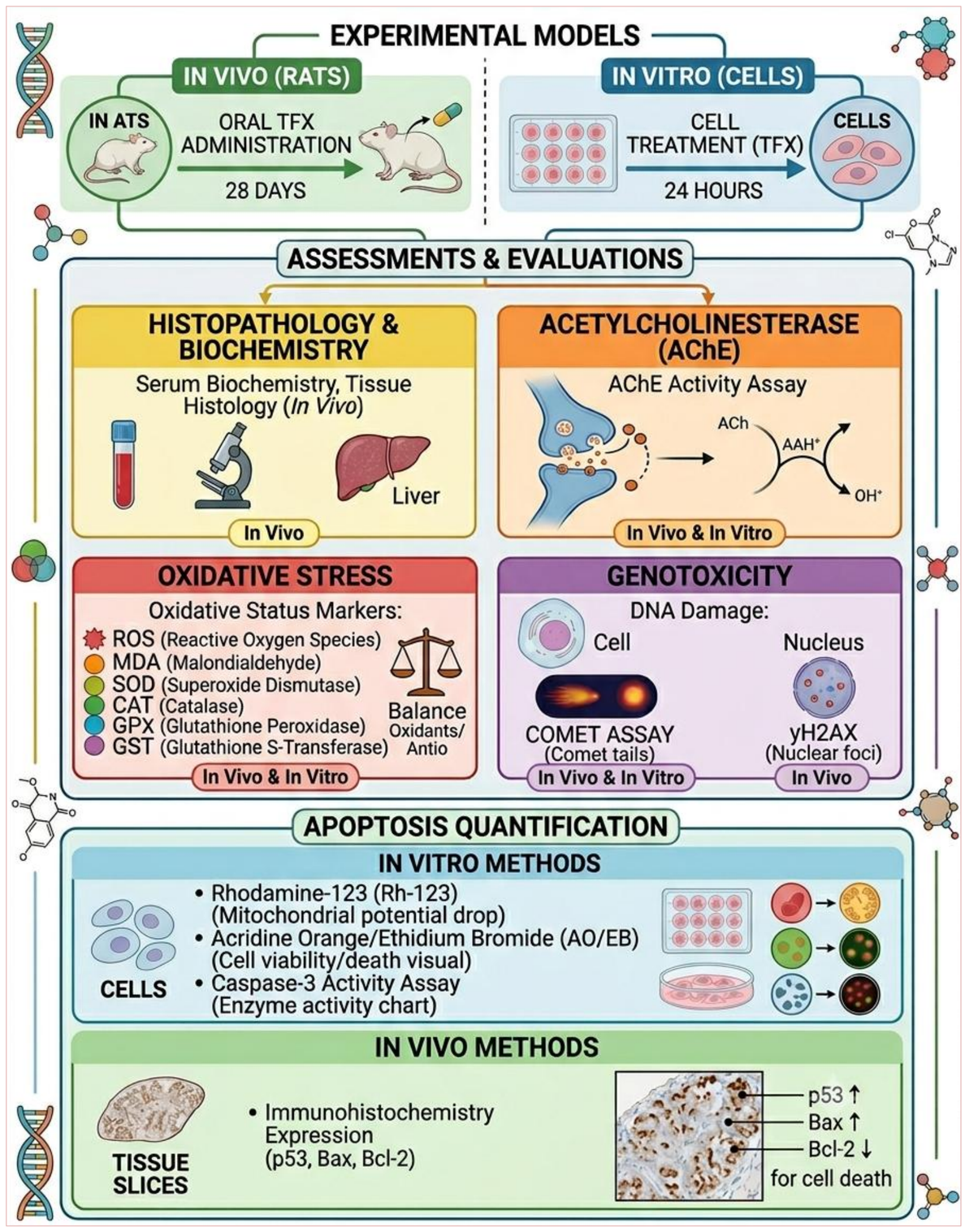
INTRODUCTION & AIM

Trifloxystrobin (TFX), a potent inhibitor of complex III within the respiratory chain, stands as one of the primary strobilurin fungicides extensively utilized across a spectrum of crops including vegetables, fruits, soybeans, and paddy fields.

In vivo studies have consistently demonstrated the vulnerability of the hepatic and renal systems to TFX exposure. In dogs and rats, TFX induces liver hypertrophy and various histopathological alterations; similarly, rat models have identified TFX-induced nephrotoxicity, characterized by increased kidney weight and renal tubule pigmentation (**EFSA, 2017**). These scientific reports from the EPA (1999) and EFSA (2017) lack a specific subacute oral NOAEL for trifloxystrobin, highlighting a toxicological paradox: low acute toxicity contrasted by subclinical effects near the systemic NOAEL. Compounded by regulatory gaps in chronic toxicity and underlying molecular mechanisms, we selected a baseline reference dose of 6 mg/kg/bw, the lowest safety threshold reported in literature. To thoroughly evaluate cellular effects around this regulatory threshold, our study utilizes four distinct doses: 3, 6, 12, and 24 mg/kg/bw (NOAEL}/2,NOAEL,NOAEL×2, and NOAEL × 4).

Despite these clear adverse effects on the liver and kidney, the exact molecular mechanisms underlying TFX-induced hepatotoxicity and nephrotoxicity in mammalian systems remain poorly understood. Therefore, this paper aims to elucidate the molecular mechanisms of trifloxystrobin nephrotoxicity and hepatotoxicity *in vivo (*Wistar rats) and *in vitro (*HEK-293T and Hep-G2).

METHOD



RESULTS & DISCUSSION

A. Phenotypic impact and biochemical impact *in vitro* and *in vivo*

Fig1. Tissue Histopathology *in vivo*

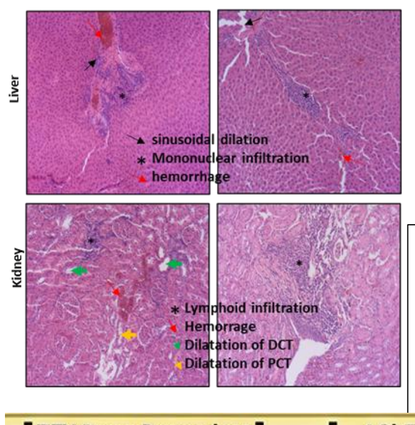


Fig2. Dose-Dependent Cytotoxicity *in vitro*

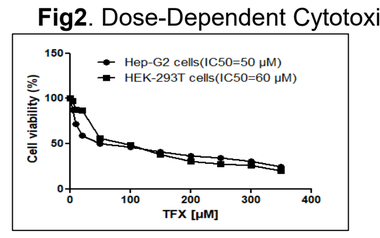


Fig3. Biochemical markers

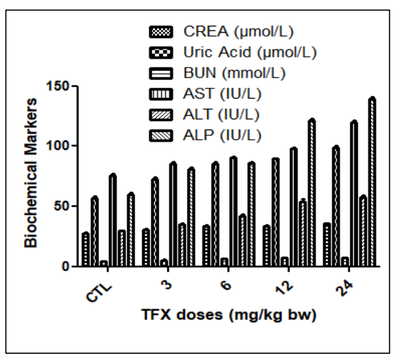
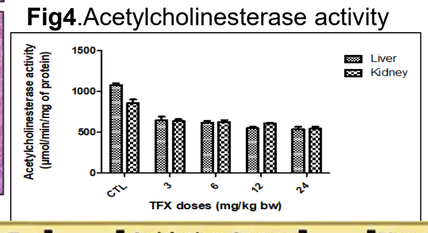


Fig4.Acetylcholinesterase activity



[TFX Dose-Dependent Exposure] → [AChE Inhibition] → [Oxidative Stress & Genotoxicity] → [Hepatotoxicity & Nephrotoxicity (Histological & Biochemicall)] → TISSUE DAMAGE

B. Molecular Mechanisms: Oxidative stress & Genotoxicity

Fig5. Oxidative Status

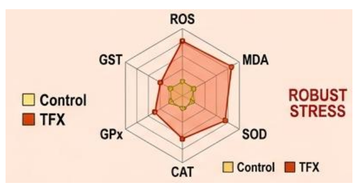
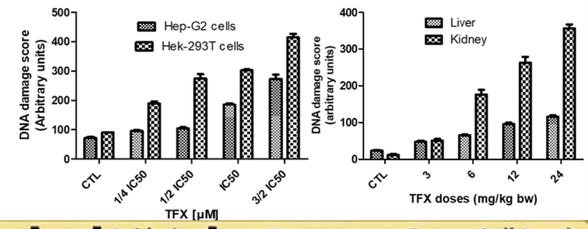


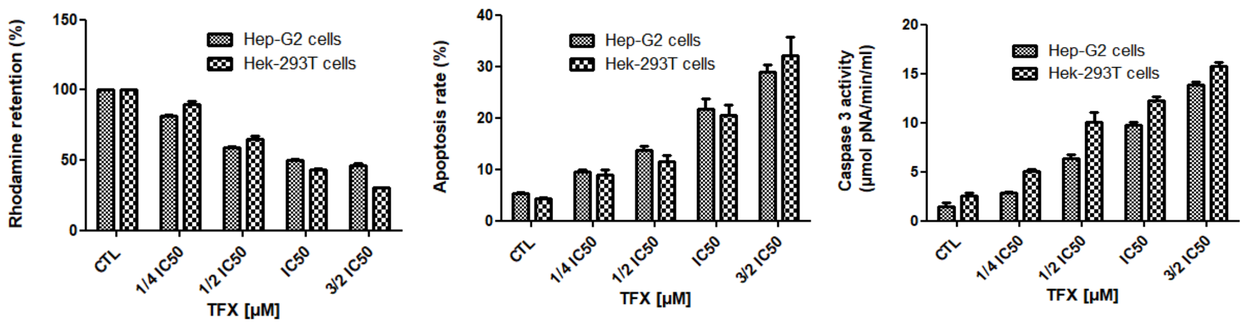
Fig6. DNA Damage in cells and in tissue



[TFX] → [Mitochondrial Dysfunction / ROS] → [Antioxidant Depletion (SOD, CAT, GPx, GST)] → [Oxidation (MDA, PC)] → [DNA Damage] → Cell Death / Apoptosis

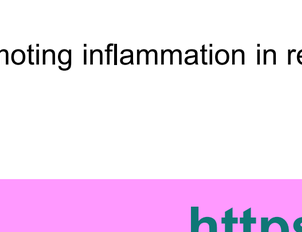
C. Apoptotic pathway & Modulation (Mitochondrial Axis) *in vivo*

Fig7. Apoptosis evaluation *in vitro*

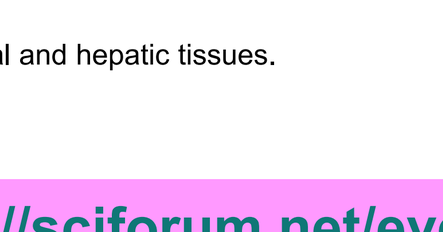


[TFX] → [Mit. Dysfunction] → [Caspase-3 Activation] → [Apoptosis (AO/EB)]

D. Apoptotic pathway *in vivo*



Illustrative IHC staining



- **Bax** and **p53** upregulation
- **Bcl2** downregulation

[TFX] → [Mitochondrial Dysfunction / ROS] → [p53 / Bax Upregulation, Bcl-2 Depletion] → [Apoptosis Hub] → [CELL DEATH / APOPTOSIS]

CONCLUSION

In conclusion, this study provides a comprehensive evaluation of Trifloxystrobin (TFX) toxicity, offering new insights into the molecular pathways that drive renal and hepatic impairment. Our research successfully bridges the gap between earlier EFSA observations and molecular reality.

FUTURE WORK / REFERENCES

Although this study confirmed TFX-induced toxicity, its potential to elicit an inflammatory response was not evaluated. Our future work aims to investigate the role of TFX in promoting inflammation in renal and hepatic tissues.