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Name of Supervisor: Prof. Imtaiyaz Hassan

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Name of Department: Centre for Interdisciplinary Research in Basic Sciences

Topic of Research: **Pharmacological inhibition of MTH1 for therapeutic management of cancer and associated diseases**

Findings

This study comprehensively investigated the therapeutic potential of targeting MutT Homolog 1 (MTH1), an enzyme that sanitizes oxidized dNTPs, thereby protecting cancer cells from oxidative DNA damage. Using structure-based drug design and virtual screening, several FDA-approved drugs and phytochemicals were screened, leading to the identification of promising MTH1 inhibitors, including Thymoquinone, Baicalin, etc. Molecular docking and dynamics simulations confirmed stable interactions with key active site residues. Biochemical assays validated their inhibitory potential, while fluorescence binding assays confirmed strong binding affinity. Furthermore, cell-based assays including MTT, apoptosis, and ROS studies in breast cancer cell lines demonstrated selective cytotoxicity and mechanistic involvement of oxidative stress-mediated apoptosis. The study also highlighted non-genetic drug resistance mechanisms linked to MTH1 overexpression, which were effectively overcome by the identified inhibitors. Collectively, the findings provide strong evidence that pharmacological inhibition of MTH1 can sensitize cancer cells to oxidative damage and represents a viable strategy for cancer therapy. The identified scaffolds hold promise for further optimization into potent, selective, and drug-like MTH1 inhibitors