PROCEEDINGS
– OF RESEARCH AND PRACTICE IN ALLIED AND ENVIRONMENTAL HEALTH –

# Psilocin as a Broad Inhibitor of CYP450 Enzymes: Integrated In Vitro and In Silico Evidence

Andreia Machado Brito-da-Costa [1,2,3,4,5], Mariana Carvalho [1,2,3], Ricardo Jorge Dinis-Oliveira [2,3,6], Áurea Madureira-Carvalho [2,7]; Sérgio F. Sousa [8,9]; Diana Dias da Silva [1*]

[1] *LAQV/REQUIMTE, ESS, Polytechnic of Porto, Porto, Portugal*
[2] *Associate Laboratory i4HB - Institute for Health and Bioeconomy, University Institute of Health Sciences - CESPU, 4585-116 Gandra, Portugal*
[3] *UCIBIO – Research Unit on Applied Molecular Biosciences, Translational Toxicology Research Laboratory, University Institute of Health Sciences (1H-TOXRUN, IUCS-CESPU), 4585-116 Gandra, Portugal*
[4] *Associate Laboratory i4HB - Institute for Health and Bioeconomy, Faculty of Pharmacy, University of Porto, Porto, Portugal*
[5] *UCIBIO – Research Unit on Applied Molecular Biosciences, Laboratory of Toxicology, Faculty of Pharmacy, University of Porto, 4050-313 Porto, Portugal*
[6] *Department of Public Health and Forensic Sciences, and Medical Education, Faculty of Medicine, University of Porto, Porto, Portugal*
[7] *UCIBIO – Research Unit on Applied Molecular Biosciences, Forensic Sciences Research Laboratory, University Institute of Health Sciences (1H-TOXRUN, IUCS-CESPU), 4585-116 Gandra, Portugal*
[8] *LAQV/REQUIMTE, BioSIM – Biomedicine Department, Faculty of Medicine, University of Porto, Porto, Portugal*
[9] *Department of Chemical Engineering, Faculty of Sciences and Technology, University of Coimbra, Coimbra, Portugal*
* *Autor correspondente: dds@ess.ipp.pt*

**Background:** Psilocybin is a psychoactive compound found in hallucinogenic mushrooms and is rapidly dephosphorylated in vivo to psilocin, its pharmacologically active metabolite. Despite the growing clinical and scientific interest in these substances, information regarding their interaction with cytochrome P450 (CYP450) enzymes remains scarce, raising concerns about potential drug–drug interactions. **Objective:** To evaluate, using combined in vitro and in silico approaches, the inhibitory potential of psilocybin and psilocin toward the human CYP2A6, CYP2B6, CYP2D6, CYP2E1, and CYP3A4 isoenzymes. **Methods:** Enzyme inhibition was assessed in vitro using fluorometric assays based on Vivid® substrates and recombinant human CYP enzymes expressed in baculosomes. Half-maximal inhibitory concentration ($IC_{50}$) values were calculated. In silico analyses comprised molecular dynamics simulations performed with the PMEMD.cuda module of AMBER16, followed by MM/GBSA binding free energy calculations, per-residue energy decomposition, and hydrogen bond analysis over the final 100 ns of stabilized trajectories. **Results:** Psilocin exhibited inhibitory activity against all evaluated isoenzymes, with $IC_{50}$ values (μM) of 2.06 for CYP2A6, 6.17 for CYP2B6, 11.89 for CYP2D6, 6.37 for CYP2E1, and 2.36 for CYP3A4. MM/GBSA results supported a strong binding affinity of psilocin, driven by specific interactions with key amino acid residues within the active sites, including stabilizing hydrogen bonds. **Conclusões:** These findings indicate that psilocin acts as a relevant inhibitor of multiple CYP450 isoenzymes, particularly CYP2A6 and CYP3A4, highlighting a potential risk for metabolic drug–drug interactions that should be considered in both clinical and toxicological contexts.

**Keywords:** drug–drug interaction; psilocin; cytochrome P450; metabolism; pharmacokinetics

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