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In vitro and *in silico* evaluation of psilocybin and psilocin's interaction with CYP450 enzymes

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Abstract

Background: Psilocybin is a hallucinogen produced by "magic mushrooms", being rapidly metabolized in the organism into psilocin [1, 2]. A scientific gap exists regarding the possible interactions between psilocybin/psilocin and CYP450 enzymes. Given their biological importance, and since the binding of drugs to CYP450 enzymes can interfere with the metabolism of other substrates leading to drug-drug interactions, this research topic is of utmost importance. **Objective**: This study aimed to evaluate *in silico* and *in vitro* the interaction of psilocybin and psilocin with the enzymes CYP2A6/2B6/2D6/2E1/3A4. **Methods:** The *in vitro* assessment of inhibition was performed using the Vivid®CYP450 screening kits. IC_{50} was calculated using GraphPad Prism 9.3.0. For *in silico* assessment, molecular dynamics were performed using the PMEMD.cuda module in AMBER16. Calculations were made on the last 100 ns of the trajectory (stable zone) to assess the interaction between enzyme and ligand, namely MMGBSA, per-residue decomposition energy, and hydrogen bonds. **Results:** Psilocin showed the capacity to be an inhibitor of CYP2A6/2B6/2D6/2E1/3A4, based on the respective IC_{50} values (μM) of 2.06, 6.17, 11.89, 6.37, and 2.36. Considering the MMGBSA, higher values were obtained for psilocin, corroborating the stronger binding affinity of this compound. The interaction of psilocybin/psilocin with CYP2A6 is mediated by a hydrogen bond established with the protein residue Asn297. Other important residues include Phe107 and Ile366. For CYP2B6, the strong binding of psilocin is mediated by interactions with Ile114, Thr302 (hydrogen bond), and Leu363. For interaction with CYP2D6, the most important residue seems to be Ser304, with which it forms a hydrogen bond; for CYP2E1, key residues include Phe207, Thr303, and Phe478. A strong hydrogen bond is formed between psilocin and CYP3A4 residue Phe304, contributing to the high binding affinity. **Conclusions:** The results suggest a potential for psilocin to inhibit all enzymes, especially CYP2A6 and CYP3A4.

Keywords: drug-drug interaction; hallucinogens; metabolism; pharmacokinetics; toxicology

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