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Inhibitory activity of psilocybin/psilocin towards the enzymes of the cytochrome P450 (CYP450): an *in vitro* evaluation

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Abstract

Background: Psilocybin is a hallucinogen produced by several “magic mushrooms” [1,2]. This prodrug is rapidly metabolized in the organism by alkaline phosphatases and esterases into psilocin, the active drug [1,2]. A scientific gap exists regarding the possible interactions between psilocybin/psilocin and CYP450 enzymes. 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 assess potential inhibitory interactions between psilocybin/psilocin and CYP3A4, 2D6, 2B6 and 2A6. **Methods:** The *in vitro* assessment of CYP450 inhibition was performed using the Vivid®CYP450 screening kits, following the user’s guide. Concentrations of psilocybin and psilocin ranged between 1.14×10^{-13} - 4 mM and 6.1×10^{-5} - 1 mM for CYP3A4; 1.71×10^{-13} - 8 mM and 6.1×10^{-5} - 1 mM for CYP2D6; 2.4×10^{-4} - 8 mM and 2.4×10^{-5} - 1 mM for CYP2B6; and 3.8×10^{-6} - 2 mM and 7.6×10^{-8} - 1 mM for CYP2A6, respectively. Each test condition was mixed with baculosomes expressing the specific CYP, Vivid® regeneration system, NADP⁺, and a non-fluorescent substrate. Solvent and positive controls of inhibition, i.e., ketoconazole (CYP3A4), quinidine (CYP2D6), miconazole (CYP2B6) and tranlycypromine (CYP2A6,) were included. Fluorescence was measured for 60 minutes (Ex=415/20nm; Em=460/20nm) and the half-maximal inhibitory concentration (IC₅₀) calculated using GraphPad prism 9.3.0. For CYP3A4 and 2D6 a minimum of three independent experiments were performed, and two independent experiments for CYP2A6 and 2B6. **Results:** For psilocybin, IC₅₀ values of 49.43 μM (CYP3A4), >1000 μM (CYP2D6 and 2B6), and >300 μM (CYP2A6) were attained. For psilocin, the following IC₅₀ values were obtained: 2.12 μM (CYP3A4), 11.89 μM (CYP2D6), 0.99 μM (CYP2A6) and 4.05 μM (CYP2B6). **Conclusions:** The results suggest a potential for psilocin to be an inhibitor of all the enzymes evaluated, especially CYP2A6, contrary to psilocybin which seems to only have the potential to inhibit CYP3A4.

Keywords: pharmacokinetics; hallucinogens; magic mushrooms

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