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Exploring the pharmacotoxicology of classic psychedelics

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Classic psychedelics such as psilocybin, psilocin, LSD, 5-MeO-DMT and mescaline have recently regained scientific relevance due to their therapeutic potential in neuropsychiatric disorders. However, significant knowledge gaps persist regarding their pharmacokinetics, toxicological profiles and safety, particularly concerning CYP450-mediated interactions, neurotoxicity, and in vivo effects. This presentation provides an integrated overview of the experimental work conducted during my PhD addressing these gaps through in vitro, in silico and in vivo approaches.

CYP450 inhibition was systematically evaluated for all compounds using Vivid® screening assays, complemented by molecular dynamics simulations. Psilocin showed inhibitory potential toward CYP2A6, 2B6, 2D6, 2E1 and 3A4, while psilocybin exhibited negligible inhibition. Among the phenethylamines and tryptamines tested, LSD and 5-MeO-DMT emerged as strong CYP2D6 inhibitors, a result corroborated in silico through high binding affinity and key stabilizing interactions with catalytic residues. These findings highlight a relevant risk for drug–drug interactions, especially considering the polymorphic nature of CYP2D6.

Neurotoxicity was assessed in SH-SY5Y cells through mitochondrial and lysosomal viability assays,

oxidative stress measurements, ATP quantification and membrane integrity evaluation. Psilocybin showed minimal cytotoxicity, whereas psilocin and LSD displayed higher toxicity, with significant ROS/RNS generation and ATP depletion observed for psilocin. Mescaline and 5-MeO-DMT demonstrated comparatively low toxicity. None of the compounds conferred neuroprotection against glutamate-induced damage.

In vivo, the behavioural effects of pure psilocybin were compared with a *Psilocybe cubensis* extract using a conditioned place preference paradigm in Wistar rats. Pure psilocybin elicited non-reinforcing or aversive responses, while the mushroom extract produced distinct behavioural patterns, suggesting that the broader bioactive matrix modulates central effects. Following behavioural assessment, tissues, fluids, and faeces were collected for histopathological, biochemical, microbiome and epigenetic analyses to further characterize systemic and neurobiological impacts.

Overall, this multidisciplinary work advances current understanding of the pharmacotoxicology of classic psychedelics by elucidating their metabolic interactions, neurotoxicological profiles and in vivo behavioural and biochemical effects, contributing essential data for both therapeutic development and toxicological risk assessment.

Short Bio

Andreia Machado Brito da Costa is a PhD student in Biomedical Sciences at CESPU, focusing on the pharmacology and toxicology of classic psychedelics. She holds a Bachelor's degree in Applied Biology from the University of Minho (2017) and a Master's degree in Forensic Sciences and Laboratory Techniques (2019). Alongside her doctoral work, she serves as a Trainee Assistant in higher education. Her research combines in vitro, in silico, and in vivo approaches to investigate CYP450 interactions, neuronal toxicity, behavioural outcomes, and broader systemic effects of compounds such as psilocybin, psilocin, LSD, 5-MeO-DMT, and mescaline. She has authored several scientific publications and contributes to funded projects aimed at advancing the pharmacotoxicological understanding of emerging psychedelic substances.

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