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Impact of psilocybin and *Psilocybe cubensis* extract on gut microbiota in Wistar Han rats

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Abstract

Background: Psilocybin, the main psychoactive compound found in *Psilocybe* mushrooms, has gained increasing attention due to its potential therapeutic effects in neuropsychiatric disorders [1]. Beyond its central effects, increasing evidence highlights the relevance of the gut–brain axis, suggesting that psychedelics may also influence intestinal microbiota composition. Whole mushroom extracts contain additional bioactive compounds that may modulate these effects, yet comparative preclinical data between pure psilocybin and mushroom extracts remain limited [2,3]. **Objective:** To evaluate the impact of pure psilocybin and *Psilocybe cubensis* extract on gut microbiota *in vivo*. **Methods:** Eighteen male Wistar Han rats (250–275 g; 8–9 weeks old) were randomly assigned to three groups (n=6): control (0.9% NaCl), psilocybin (3 mg·kg^{-1}), and *P. cubensis* extract (equivalent to 3 mg·kg^{-1} psilocybin/psilocin). Treatments were administered by oral gavage (0.5 mL·kg^{-1}). Fecal samples were collected at baseline (T1) and at days 7 (T7) and 14 (T14) post-exposure for microbiota analysis. Microbial profiling was performed using long-read amplicon sequencing targeting the full-length 16S rRNA gene. Libraries were prepared using SMRTbell technology and sequenced on the PacBio platform. Bioinformatic analysis enabled high-resolution taxonomic assignment and reconstruction of microbial community structure, improving species-level identification accuracy. Statistical analysis included ANOVA and multivariate analysis of beta-diversity (p<0.05). All procedures were approved by the institutional Animal Welfare Committee and DGAV, in accordance with European and national legislation. **Results:** Baseline microbiota composition (T1) was similar across all groups, clustering closely together, as expected prior to treatment. This profile remained comparable to the control group at T7 and T14. In contrast, distinct shifts in microbial community structure were observed in treated groups. Both psilocybin and *P. cubensis* extract induced separation from baseline and control profiles at T7, with further divergence at T14. This effect was more pronounced in the psilocybin group, which exhibited the greatest distance in cluster analysis, indicating a stronger impact on microbiota composition. **Conclusions:** These findings suggest a time-dependent modulation of gut microbiota induced by both treatments, with differential magnitude between the pure compound and the whole extract.

Keywords: psilocybin; gut microbiota; psychedelics

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