PsiloBiota - how compounds found in *Psilocybe* mushrooms may affect our brain through interaction with the gut microbiota.

For decades, research on fruiting bodies of psilocybin-containing mushrooms was severely constrained by legal and social barriers, which has left our knowledge of their components and pharmacological effects highly limited. Only recently has psilocybin, a compound present in certain species of *Psilocybe*, been reexamined, and its potential clinical application in the treatment of therapy-resistant depression discovered. However, it remains unknown why a single dose of psilocybin can produce long-lasting therapeutic effects, as well as what the chemical structure and pharmacological properties of other compounds found in *Psilocybe* mushrooms are.

The PsiloBiota project posits that fruiting bodies of *Psilocybe* mushrooms contain numerous, as yet unidentified, natural products that may act on the brain through the gut-microbiota-brain axis. This axis is a network of interactions between intestinal microorganisms, the digestive system, and the nervous system, influencing central nervous system functions and playing a key role in the regulation of mood and cognition.

Within the project, the research team will:

- identify and describe active compounds present in collected and/or cultivated fruiting bodies of *Psilocybe* mushrooms,
- investigate how gut microorganisms transform these compounds into new molecules and how they affect the composition of the human gut microbiota,
- evaluate the impact of selected compounds on the functioning of the intestinal barrier, the blood-brain barrier, and neuroinflammatory processes in *in vitro* models,
- test their effects in an *in vivo* model of depression, with particular attention to the microbiota-gut-brain axis.

Combining advanced chemical, microbiological, and neurobiological studies will make it possible to uncover new mechanisms of action for compounds found in *Psilocybe* fruiting bodies as well as help explain the remarkable effectiveness of psilocybin in the treatment of drug-resistant depression. The results will also point toward entirely new therapeutic targets, not only for depression but also for other disorders linked to central nervous system function. Furthermore, insights into interactions with the gut microbiota will serve as a foundation for developing strategies to enhance psilocybin therapy through personalized modulation of patients' microbiomes.

The PsiloBiota project will open a new chapter in research on *Psilocybe* mushrooms, contributing to the ongoing renaissance of studies on psychoplastogens- compounds offering groundbreaking therapeutic opportunities for mental and neurodegenerative disorders resistant to conventional treatments.