Different types of magic mushrooms use unique biochemical paths to produce the same active compound

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Psilocybe cubensis grows worldwide in tropical and subtropical regions, including Central and South America, Southeast Asia, and Oceania. The mushroom prefers moist, fertilizer-rich soils and contains the psychoactive substance psilocybin, which is currently being researched as an active compound for the treatment of therapy-resistant depression. Credit: Felix Blei, Leibniz-HKI

A German-Austrian team led by Friedrich Schiller University Jena and Leibniz-HKI has been able to biochemically demonstrate for the first time that different types of mushrooms produce the same mind-altering active substance, psilocybin, in different ways.

Both Psilocybe mushrooms and fiber cap mushrooms of the genus Inocybe produce this substance, but use completely different enzymes and reaction sequences for this process. The results are published in *Angewandte Chemie International Edition*.

"This concerns the biosynthesis of a molecule that has a very long history with humans," explains Prof. Dirk Hoffmeister, head of the research group Pharmaceutical Microbiology at Friedrich Schiller University Jena and the Leibniz Institute for Natural Product Research and Infection Biology (Leibniz-HKI).

"We are referring to psilocybin, a substance found in so-called 'magic mushrooms,' which our body converts into psilocin—a compound that can profoundly alter consciousness. However, psilocybin not only triggers psychedelic experiences, but is also considered a promising active compound in the treatment of therapy-resistant depression," says Hoffmeister.

Two paths, one molecule

The study, which was conducted within the Cluster of Excellence "Balance of the Microverse," shows for the first time that fungi have developed the ability to produce psilocybin at least twice independently of each other. While Psilocybe species use a known enzyme toolkit for this purpose, fiber cap mushrooms employ a completely different biochemical arsenal—and yet arrive at the same molecule.

This finding is considered an example of convergent evolution: Different species have independently developed a similar trait, but the magic mushrooms have gone their own way in doing so.

Two paths lead to the same molecule: Independently of each other, different genera of "magic mushrooms" have developed two different enzyme pathways that produce the same psychoactive substance, psilocybin—a rare example of convergent evolution in natural product biosynthesis. Credit: Tim Schäfer, Leibniz-HKI

Searching for clues in fungal genomes

Tim Schäfer, lead author of the study and doctoral researcher in Hoffmeister's team, explains, "It was like looking at two different workshops, but both ultimately delivering the same product. In the fiber caps, we found a unique set of enzymes that have nothing to do with those found in Psilocybe mushrooms. Nevertheless, they all catalyze the steps necessary to form psilocybin."

The researchers analyzed the enzymes in the laboratory. Protein models created by Innsbruck chemist Bernhard Rupp confirmed that the sequence of reactions differs significantly from that known in Psilocybe.

"Here, nature has actually invented the same active compound twice," says Schäfer.

However, why two such different groups of fungi produce the same active compound remains unclear. "The real answer is that we don't know," emphasizes Hoffmeister. "Nature does nothing without reason. So there must be an advantage to both fiber cap mushrooms in the forest and Psilocybe species on manure or wood mulch producing this molecule—we just don't know what it is yet."

"One possible reason could be that psilocybin is intended to deter predators. Even the smallest injuries cause Psilocybe mushrooms to turn blue through a chemical chain reaction, revealing the breakdown products of psilocybin. Perhaps the molecule is a type of chemical defense mechanism," says Hoffmeister.

More tools for biotechnology

Although it is still unclear why different fungi ultimately produce the same molecule, the discovery nevertheless has practical implications.

"Now that we know about additional enzymes, we have more tools in our toolbox for the biotechnological production of psilocybin," explains Hoffmeister.

Schäfer is also looking ahead, stating, "We hope that our results will contribute to the future production of psilocybin for pharmaceuticals in bioreactors without the need for complex chemical syntheses."

At the Leibniz-HKI in Jena, Hoffmeister's team is working closely with the Bio Pilot Plant, which is developing processes for producing natural products such as psilocybin on an industry-like scale.

At the same time, the study provides exciting insights into the diversity of chemical strategies used by fungi and their interactions with their environment.

More information: Dissimilar Reactions and Enzymes for Psilocybin Biosynthesis in Inocybe and Psilocybe Mushrooms, *Angewandte Chemie International Edition* (2025). DOI: 10.1002/anie.202512017

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