# Psychedelic compound from magic mushrooms produced in yeast

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Scientists from DTU Biosustain prove that psilocybin, a potential drug for treating depression and other psychological conditions can be produced in yeast. Credit: The Novo Nordisk Foundation Center for Biosustainability

Psilocybin mushrooms have been found to have minimal harmful effects and could potentially benefit those with depression. But they remain illegal even though they offer a groundbreaking alternative to several under-treated psychological conditions.

Nevertheless, psychedelics are currently riding a wave of positive momentum brought on by cannabis, and if psilocybin gets approved as a pharmaceutical drug, production in yeast appears to be the most commercially viable option.

"It's unfeasible and way too expensive to extract psilocybin from magic mushrooms and the best chemical synthesis methods require expensive and difficult to source starting substrates. Thus, there is a need to bring down the cost of production and to provide a more consistent supply chain," says Nick Milne, former Postdoc at DTU Biosustain and CSO and Co-founder of Octarine Bio.

Bio-based production of psilocybin has garnered major interest and researchers have already proved small-scale production in E. coli. However, production in bacteria comes with a wide range of concerns which can be addressed by using yeast instead.

In yeast, the scientists prove that psilocybin can be produced de novo, which means that you can produce the molecule by simply growing the yeast with sugar and other nutrients, without the need to add any other starting substrates.

Producing psilocybin de novo in E. coli is difficult since a key enzyme in the biosynthetic pathway doesn't work in bacteria, and so to get around this problem you need to add an expensive starting substrate, making the whole production process too costly.

"Since yeast and Psilocybe mushrooms are quite closely related species, this enzyme works very well in yeast, providing a much more cost-efficient alternative," says group leader at DTU Biosustain Irina Borodina.

Additionally, yeast also performs better in large-scale fermentation due to its long history in the beer brewing process, and also in the purification process since E. coli produces additional potentially harmful compounds that you would not like to have in your final product.

**Challenges still to be solved**

In the study published in Metabolic Engineering Journal, the researchers reached fairly high titers, but if production should be scaled up, one major obstacle needs to be overcome.

On psilocybin's core skeleton sits a phosphate group which is cleaved off when the molecule is converted to its active form.

"What we find in the study is that we get a lot of this non-phosphorylated compound psilocin.

Essentially, we are losing half of our product because the phosphate group falls off. Dealing with this high amount of psilocin is something that absolutely needs to be solved before realistically moving to a production process," explains Nick Milne.

To fix the issue, a lot more metabolic engineering needs to be done. The good thing for the scientists is that the starting point is a well-studied pathway called the shikimate pathway. There is already a lot of experience working with it, so from that point of view, it should be pretty straight forward.

**The valuable derivatives**

While de novo production of psilocybin in yeast in these titers should be considered impressive as a proof of concept, the researchers behind the study also underline the importance of producing other natural and novel derivatives.

Psilocybe mushrooms also produce a range of molecules that are structurally similar to psilocybin but are too difficult to purify, making research into their therapeutic effect difficult. In this study, the researchers demonstrated the production of a range of psilocybin pathway derivatives, and further, by combining genes from the melatonin biosynthetic pathway, could demonstrate the production of a completely novel molecule.

This technology has been transferred to Octarine Bio, a spin-out company from The Novo Nordisk Foundation Center for Biosustainability (DTU Biosustain) and the University of Copenhagen, who are interested not only in the large-scale production of psilocybin but also the potential of producing new derivatives.

"Our interest is not only to make kilogram scale production of psilocybin but to use the biological machinery to make new derivatives that aren't available today. Thus, it is very useful that we could not only demonstrate the production of psilocybin but also find many derivatives that could turn out to have important therapeutic relevance," says Nick Milne.

**More information:** N. Milne et al, Metabolic engineering of Saccharomyces cerevisiae for the de novo production of psilocybin and related tryptamine derivatives, *Metabolic Engineering* (2020). DOI: 10.1016/j.ymben.2019.12.007

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