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Simple sugar could soon compete with glyphosate

For many decades, glyphosate has been a common component of agricultural pesticides worldwide, although it is a controversial herbicide that may be harmful for humans, animals and the environment. The good news is that a more sustainable alternative is now in sight: researchers from the University of Tübingen have discovered a sugar molecule called 7-deoxy-sedoheptulose (7dSh). 7dSh inhibits the growth of plants and microorganisms, but appears to be completely harmless to human cells. Long-term studies are now being undertaken to substantiate this finding.

Modern, high-performance agriculture is virtually unthinkable without weed killers. Glyphosate is one of the most common active ingredients of weed killers and hundreds of thousands of tons of glyphosate are produced worldwide every year. All plants – with the exception of those genetically modified organisms that have been bred for resistance to this herbicide – die within a very short time after exposure to the toxin. Despite its efficiency in killing weeds, the use of glyphosate is highly controversial because of studies that have shown an association of the chemical with human disease. In 2015, the International Agency for Research on Cancer concluded that glyphosate is "probably carcinogenic to humans". Other authorities and organisations disagreed with the IARC, and glyphosate was eventually reapproved in the EU in 2017.

The microbiologist Dr. Klaus Brilisauer has discovered an unusual sugar molecule produced by cyanobacteria that might soon be able to make the use of glyphosate obsolete. This newly discovered sugar has no harmful side effects on humans and the environment.

A research team from the University of Tübingen has now discovered a natural substance that might become an alternative to the controversial weed killer: a simple but unusual cyanobacterial sugar molecule that inhibits the growth of microorganisms and plants, but is harmless to human cells. The study was conducted by Dr. Klaus Brilisauer and Prof. Dr. Karl Forchhammer from the Interfaculty Institute for Microbiology and Infection Medicine and Prof. Dr. Stephanie Grond from the Institute of Organic Chemistry.*

Sugar molecule acts as antimetabolite

A number of years ago, the scientists from Tübingen observed that cyanobacteria are able to inhibit the growth of other microorganisms. However, at the time they did not investigate this any further. During his doctoral research work, microbiologist Klaus Brilisauer eventually discovered the reasons for the cyanobacteria's growth-inhibiting capabilities, i.e. a sugar molecule called 7-deoxy-sedoheptulose (7dSh). "It is quite surprising that a natural product like this sugar has such a simple chemical structure," explained the researcher. "Initially, despite the simplicity of the molecule, elucidating its structure with NMR (nuclear magnetic resonance spectroscopy) proved to be quite difficult. Nevertheless, we soon understood that the sugar consisted of seven carbon atoms. We now want to synthesize the substance in order to substantiate this idea. However, chemists have suggested that it would be far too complicated to chemically synthesize the molecule."

Chemical structure of 7-deoxy-sedoheptulose (7dSh)

Brilisauer did not accept that this was the case and went back to the drawing board to find out how he could isolate the natural product. He eventually managed to isolate an enzyme called transketolase from cyanobacterial cultures, which enabled him to work as closely to the biological system as possible. His attempts to produce 7dSh with the help of the transketolase enzyme were successful. "In fact, 7dSh synthesis worked quite well," said the researcher. "We are now even able to produce a 7dSh precursor consisting of five carbons from normal ribose, which is a whole lot cheaper than isolating 7dSh from cyanobacteria. And interestingly enough, we eventually found that the synthesis of 7dSh in bacteria is no different from what happens in our test tubes. Quite amusing really." The scientists are already able to produce several milligrammes of pure 7dSh. The transketolase enzyme transfers a C2 group to a C5 sugar known as 5-deoxy-ribose, resulting in the sought-after C7 sugar. This method is referred to as chemoenzymatic synthesis.

Inhibited metabolic pathway does not exist in humans and animals

Seedlings of Arabidopsis thaliana after germination and 7-day cultivation. While the control group developed normally, exposure to 250 µg glyphosate or 7dSh resulted in the significant inhibition of growth (scaling is identical in all images).

The researchers took the synthesized sugar and went on to elucidate the molecular principle of growth inhibition. They treated cyanobacteria with 7dSh and examined them using mass spectrometry. "We found that a specific substance accumulated somewhere during the metabolic process," reports Brilisauer. "This provided us with information about the site of action, i.e. that 7dSh blocks an enzyme of the shikimate pathway, namely dehydroquinate synthase (DHQS), which mistakes 7dSh for the "correct" substrate. This inhibits the enzyme's activity and leads to a standstill in the metabolic pathway. The interesting thing is that the shikimate pathway occurs in plants and microorganisms, but not in humans and animals."

Enzymes of the shikimate pathway are in general very attractive targets for substances that inhibit the growth of weeds: the controversial weed killer glyphosate is hitherto one of the best-known herbicides. In contrast to glyphosate, 7dSh is a pure natural product. Initial investigations have already proven that the substance is harmless for humans and animals. "To find out more, we treated human cell lines with extremely high 7dSh concentrations to make sure the sugar did not have a toxic effect, and it proved to be completely harmless," says Brilisauer.

In addition, the researchers exposed zebrafish embryos to 7dSh to test its ecotoxic effect on aquatic organisms. Again, the substance proved to be completely harmless. "There is a great deal of evidence that there are no detrimental effects on humans and animals, even if the sugar is applied in high concentrations to fields," says the biologist. "In addition, the cyanobacteria have been producing this substance for millions of years without any effect on the environment. Although we have not done any large-scale animal experiments because so far everything has been basic research, we are very positive."

Search for suitable cooperation partners is underway

The natural 7dSh sugar was isolated from the freshwater cyanobacterial species "Synechococcus elongatus"

However, it is certain that 7dSh sustainably inhibits the growth of plants. "It seems as if plants absorb the sugar via their roots; it has to be taken up actively, which is why it is probably not possible to spray the active ingredient solely on leaves," says Brilisauer. "However, we are not herbicide researchers and this needs to be clarified in cooperation with experts. There are certainly aids that facilitate the uptake of the substance. However, it goes without saying that you have to find a substance that is also environmentally friendly."

Both the industry and academia have expressed great interest in cooperating with the researchers from Tübingen. Brilisauer comments: "The University of Tübingen has filed a patent, now we have to find suitable cooperation partners so we can continue to work effectively. There are still a number of questions to clarify: for example, how the substance is taken up into the cells and whether one can produce chemical derivatives. At the same time, of course, we have to review the environmental behaviour of the substance in long-term studies. Of course, we very much hope that 7dSh will be able to find its way from the lab to the field in maybe two or three years' time. We are really positive that it will work - our data are highly promising."

Reference:

* Brilisauer, K., Rapp, J., Rath, P., Schöllhorn, A., Bleul, L., Weiß, E., ... & Forchhammer, K. (2019). Cyanobacterial antimetabolite 7-deoxy-sedoheptulose blocks the shikimate pathway to inhibit the growth of prototrophic organisms. Nature Communications, 10(1), 545, https://doi.org/10.1038/s41467-019-08476-8

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Dr. Petra Neis-Beeckmann

Further information

Dr. Klaus Brilisauer
Universität Tübingen
Institut für Mikrobiologie/ Institut für Organische Chemie
Auf der Morgenstelle 28
72076 Tübingen

Phone: +49 (0)7071 29-74642
E-mail: klaus.brilisauer(at)uni-tuebingen.de

- Eberhard Karls University Tübingen

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