Natural substance with herbicide potential

The same but different: What makes sugar 7Sdh a better herbicide?

The sugar 7-deoxy-sedoheptulose (7dSh) is produced by cyanobacteria and inhibits the same metabolic pathway as the broad-spectrum herbicide glyphosate, thus making it an excellent herbicide candidate. Despite this amazing similarity, the microbiologist who discovered 7dSh, Prof. Dr. Karl Forchhammer, believes that this sugar has clear ecological advantages over glyphosate. In an interview with Rebecca Debo, he told us what the advantages are and what difficulties had to be overcome on the way to isolating the sugar molecule.

The publication of your discovery made such massive waves back in April 2019. Did you expect this huge media response?

The biogenic sugar 7dSh was isolated from cyanobacteria and its herbicidal effect described for the first time in the working group of Prof. Dr. Karl Forchhammer at the University of Tübingen.
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Forchhammer: No, not at all, we were taken totally by surprise. I have made much more significant discoveries in basic research, and hardly anyone was interested in them. And suddenly a side project turns into such a big thing. Afterwards, I realised why we were getting so much attention. At the time when our discovery became known, the subject of glyphosate was very much in the media spotlight: Bayer had just taken over Monsanto, and the further approval of glyphosate was already under discussion.

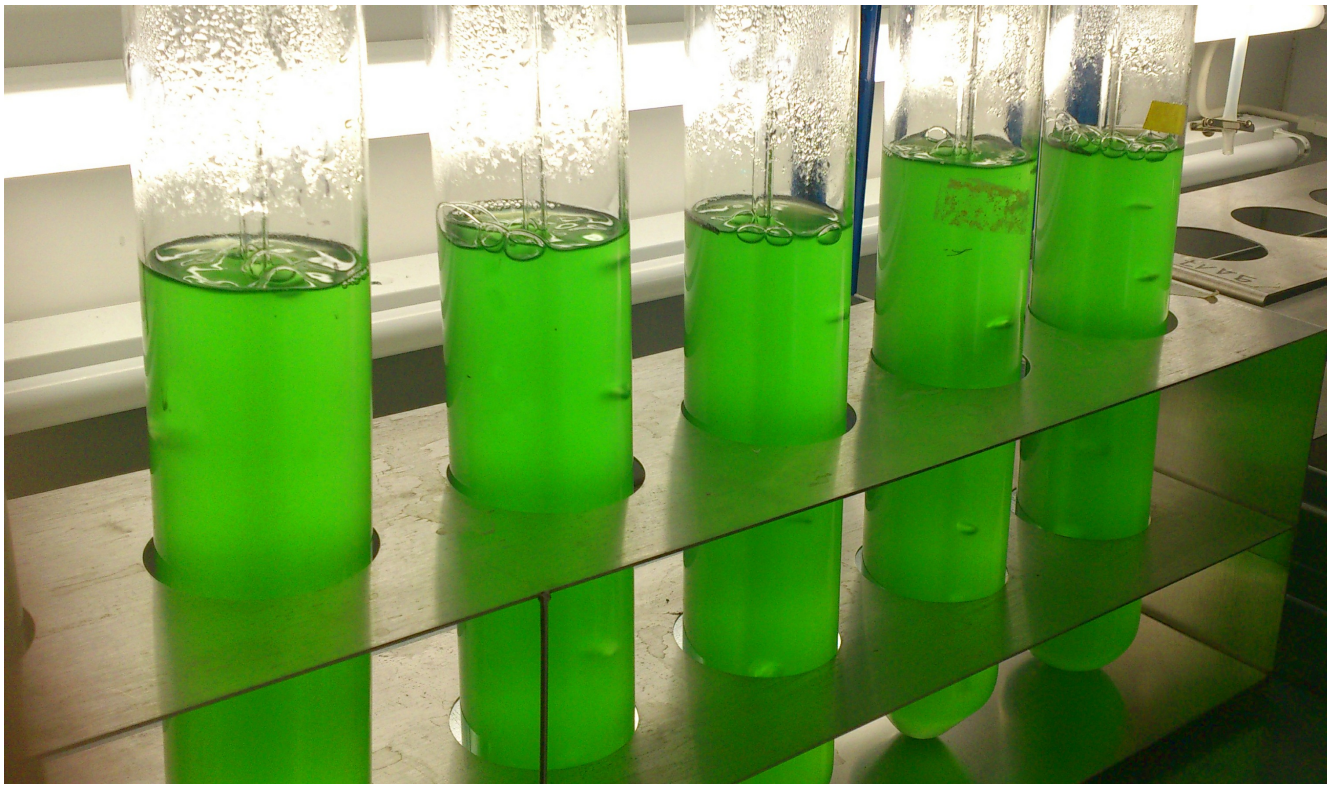
Also, there are no alternatives. Glyphosate simply works incredibly well - if it weren't for the side effects, notably for the environment. Glyphosate is ruining its own success because it is being used to excess. Even if most of it were degraded, non-degradable by-products would remain in the environment. There is no way to prevent this, given the quantities that are spread on the fields. In the context of this debate, our discovery looked as if we were offering a way out of this deadlock.

Your discovery, the sugar 7-deoxy-sedoheptulose (7dSh), is a natural substance. Is it common to find natural substances with this kind of application potential?

Forchhammer: No, it does not happen often. Something like this is a chance find that nobody expected. These days it is very difficult to find new substances. Almost all substances that are being discovered have been described before. Our substance was also described by a Japanese working group in the early 1970s. At that time, no one knew what it was good for. We have now been able to show that the substance has an inhibitory effect on other cyanobacteria and prevents Arabidopsis seeds from germinating.

Regarding the discovery itself: how exactly did the isolation of the sugar work, and what was the biggest challenge?

Forchhammer: Standard working protocols are suitable for isolating relatively hydrophobic substances. However, we were



The natural substance 7dSh was isolated from cultures of the freshwater cyanobacterium Synechococcus elongatus.
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dealing with an unknown substance that always roared through the column. Then we realised that it might be a polar substance. Using appropriate methods, Klaus Brilisauer (Prof. Forchhammer's former doctoral student, editor's note) was slowly able to work his way through the problem and finally obtain active fractions containing fewer and fewer molecules. Mass spectroscopy can, for example, be used to analyse an active fraction and find out how complex a mixture still is. The aim is to purify the mixture until it contains only one substance. This process took almost two years and was actually the most difficult part.

The next step was to obtain a molecular formula from the mass. NMR (nuclear magnetic resonance spectroscopy, editor's note) is used for this purpose. Using NMR spectra, our partner from the Department of Organic Chemistry, Prof. Grond, was able to determine which molecule it was.

How were you able to determine the effect of the sugar?

Forchhammer: We then knew that the substance was a sugar and that it inhibits some cyanobacteria. But we did not yet know the inhibitory mechanism of the sugar, or that it had potential as a herbicide. To find out the exact site of the sugar's action, we compared the metabolites (intermediates or breakdown products formed in a cell by metabolic processes, editor's note) of cyanobacteria that were exposed to the sugar and those that were not, and did something called a non-targeted metabolic analysis. This involves analysing and comparing all metabolites. Only the peaks that differ in treated and untreated cells are considered. We found that a specific molecule accumulated massively at the beginning of the shikimate pathway, i.e. in the metabolic pathway that leads to aromatic amino acids. From then on, it was clear: if this molecule accumulates, then it must be our target.

When I heard that this substance inhibits the shikimate pathway, I immediately realised that we had probably found a substance with valuable herbicidal activity. That's because glyphosate inhibits the same metabolic pathway, but at a slightly different place.

Nevertheless, you are already talking about a major advantage of this sugar over glyphosate. What exactly is this advantage?

Forchhammer: Our sugar is a natural substance that has probably been produced over millions of years. Other organisms have since been confronted with this substance in the environment. And there is practically no natural substance that is not degradable. For reasons of plausibility alone, there must therefore be many soil bacteria that can metabolise this substance in a flash. And also from our first preliminary studies it looks as if the substance disappears into the soil relatively quickly.

We have also carried out a comparative study with Prof. Dr. Köhler (Institute of Ecology and Evolution, University of Tübingen) in which the effect of glyphosate and 7dSh on zebrafish embryos was compared. We did not measure any negative effect of our sugar on the fish.

Microbiologist Dr. Klaus Brilisauer has discovered an unusual sugar molecule that is produced by cyanobacteria and may soon be able to compete with glyphosate - without harmful side effects on humans and the environment.

Glyphosate, like your sugar, inhibits the shikimate pathway, which is not only present in bacteria and plants, but also in archaea, protozoa and many algae and fungi. For this reason alone, glyphosate also has a major impact on biodiversity. Do you think your sugar has a similar effect?

Forchhammer: Glyphosate has a strong impact on biodiversity due to a relatively long soil retention time. The longer the substance remains in the soil, the stronger its effect on biodiversity. Since our sugar is thought to have a short soil retention time, I can imagine that the effect on biodiversity would be much milder.

You produce the sugar using chemoenzymatic synthesis. What exactly does this mean?

Forchhammer: Chemoenzymatic synthesis means that chemical reactions are coupled with enzymatic reactions. The problem with sugar molecules is that it is not possible to produce them in their pure chemical form. Sugars are very complex due to their stereochemistry. Each attached group can stick out in different directions, rather like branches sticking out of a tree trunk, and this influences the sugars' biological effect. If just one group has the wrong stereochemistry, the sugar loses its effect. We have also tested this with our substance and produced different 7dSh stereoisomers. The stereoisomers of the sugar did not have a herbicidal effect.

We now have a process that enables us to produce 7dSh. Two precursors are needed for the synthesis, a biologically produced C5 sugar and chemically produced hydroxypyruvate. A transketolase enzyme produces the final substance in the final reaction step.

What are the next steps in the development from sugar to herbicide?

Forchhammer: So far, we know that the effect on germinating plant seeds is particularly strong, which is probably due to the efficient sugar uptake of the seedlings. The difficulty is to find a way for a more developed plant to be able to take up the substance. A few experiments have been done in this area, but there has been no major breakthrough as yet. That is why we have applied for BMBF funding for a follow-up project with other cooperation partners, which will focus on precisely this further development of the sugar.

The effect of the sugar has been clarified. Now the question is how the sugar can be turned into a herbicide. Because the sugar is not yet a herbicide: if you simply apply the sugar to a plant from the outside, this does not necessarily have an inhibitory effect.

How do you assess the economic future of the sugar?

Forchhammer: Producing the sugar is not cheap of course, and this is currently a major hurdle for the industry. But if we believe that the substance is useful and can contribute to more sustainable agriculture, then it is actually in all our interests

to use it. But this can only be done with an industrial partner who is willing work alongside us.

Thank you very much for the interview.

Article

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Further information

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- Neues, biogenes Herbizid patentiert - ein Beitrag zur weltweiten Ernährungssicherheit
- Simple sugar could soon compete with glyphosate
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