



Medicine

Nature's pharmacy – plant-based active substance kills renal cancer cells

Extracted from the *Phyllanthus engleri* tree, englerin A kills the cancer cells by increasing their calcium concentration

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Nature holds many compounds in store that are of great value to medical research. Recently, for example, scientists discovered that a substance contained in an African shrub kills cancer cells in the kidney. Together with colleagues from Berlin and Leeds, researchers from the Max Planck Institute of Molecular Physiology in Dortmund discovered that the molecule known as englerin A significantly increases the concentration of calcium in cells, causing the cancer cells to die. Englerin A only activates the calcium channels of renal cancer cells, but not those of healthy cells. In cooperation with the Lead Discovery Center in Dortmund, the scientists now want to find out whether englerin A could potentially be used as an innovative drug to treat renal cancer in the future.



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*The bark of *Phyllanthus engleri* contains a chemical, Englerin A, a substance which kills kidney cancer cells.*

In its native habitat in southern Africa, *Phyllanthus engleri* has long been known to have medicinal properties. The shrub or small tree, which was formerly classified as belonging to the spurge family, is most commonly found in the dry savannahs of Tanzania, Zambia, Malawi, Zimbabwe, Mozambique and South Africa. In Tanzania, for example, the plant's roots are used to treat epilepsy, and chewing the leaves and fruits is said to alleviate coughs and stomach aches. A decoction made from the roots is even said to be effective against bilharziosis and gonorrhoea. At the same time, the plant also contains strong toxins that can cause lethal poisoning.

In 2009, American scientists isolated more than 30 substances found in *Phyllanthus engleri* and tested their efficacy on cancer cells. They discovered that a specific type

of compound taken from the bark of the tree – a variant known as (–)-englerin A – is particularly effective against renal cancer cells and some other forms of cancer. That same year, the group led by Mathias Christmann, who now conducts research at the Freie Universität Berlin, synthesised this complex compound. The precursor they used is the primary constituent in the essential oil of catnip (*Nepeta cataria*): nepetalactone – a substance that causes cats to lapse into a state of ecstasy. Nepetalactone is therefore a renewable raw material extracted from a plant that is more readily available than *Phyllanthus engleri*. This is decisive for the further use of englerin A, as it means that larger amounts of the substance can be produced.

However, exactly how englerin A kills cancer cells remained a mystery. Until recently, it was believed that englerin A might target a variant of the enzyme protein kinase C. The Max Planck scientists have now discovered though that cells that respond to englerin A particularly well do not contain this type of enzyme at all. Instead, the researchers focused on a family of calcium channels known as TRPCs (canonical *transient receptor potential channels*), which are found in the membranes of renal cells.

Different renal cancer cells form different numbers of these channels. The measurements showed that adding englerin A causes the calcium concentration inside these cells to rise so significantly that the cells die within a few minutes. “We studied cancer cells that produce a lot of TRPC4. These cells are particularly sensitive to englerin A. In cells that do not produce any TRPC4 or only produce normal amounts, the calcium levels do not rise as much. Therefore, these cells don’t die,” explains Slava Ziegler from the Max Planck Institute of Molecular Physiology. However, the researchers still do not know whether the overproduction of TRPCs is the sole cause of the dying off of the cancer cells.

Englerin A thus acts specifically on cancer cells in the kidney. “This property gives the substance a major advantage over other anti-cancer drugs, because it means the side effects afflicting healthy cells could possibly be prevented,” says Herbert Waldmann from the Max Planck Institute in Dortmund, where, among other topics, he conducts research into the use of naturally occurring substances in the development of active agents.

Together with the Lead Discovery Center in Dortmund, the researchers now want to determine whether englerin A is suitable as an anti-cancer drug. The Center, which was founded by the Max Planck Society, helps bring potential active agents from basic research to clinical trial. “Englerin A is a prime example of an active substance that harbours great potential, but also a significant risk. In the current phase there would be hardly any commercial partners willing to provide the funding for further studies. The Lead Discovery Center can bridge this gap between basic research and medicine,” says Waldmann.

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