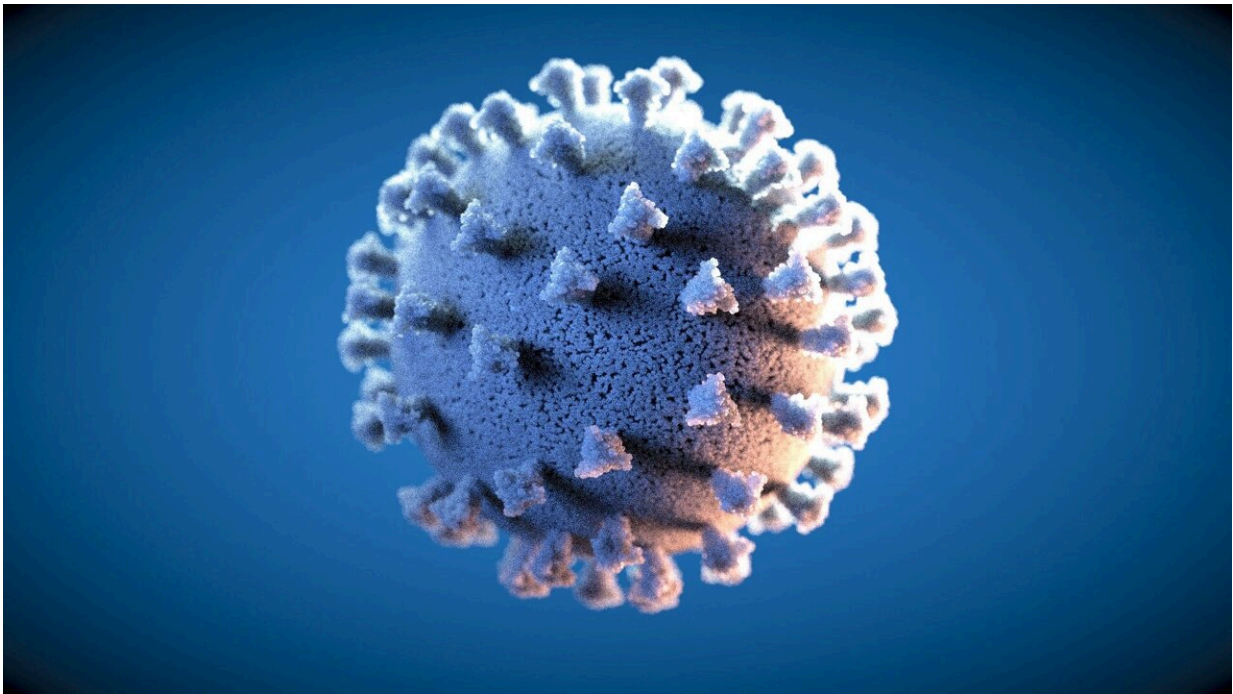


Natural substances show promise against coronavirus

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Artistic representation of the coronavirus. Credit: Science Communication Lab for DESY

Three natural compounds present in foods such as green tea, olive oil and red wine are promising candidates for the development of drugs against the coronavirus. In a comprehensive screening of a large library of natural substances at DESY's X-ray source PETRA III the compounds bound to a central enzyme vital for the replication of the coronavirus.

All three compounds are already used as active substances in existing drugs, as the team headed by Christian Betzel from the University of Hamburg and Alke Meents from DESY reports in the journal *Communications Biology*. However, if and when a coronavirus drug can be developed on the basis of these compounds remains to be investigated.

"We tested 500 substances from the Karachi Library of Natural Compounds if they bind to the papain-like [protease](#) of the novel coronavirus, which is one of the main targets for an antiviral drug," explains the study's main author Vasundara Srinivasan from the University of Hamburg. "A compound that binds to the enzyme at the right place can stop it from working."

The papain-like protease (PL^{pro}) is a vital enzyme for virus replication: When a cell is hijacked by the coronavirus, it is forced to produce building blocks for new virus particles. These proteins are manufactured as a long string. PL^{pro} then acts like a molecular pair of scissors, cutting the proteins from the string. If this process is blocked, the proteins cannot assemble new virus particles.

"However, PL^{pro} has another vital function for the virus," says Srinivasan. "It blocks a protein of the immune system, called ISG15, and that severely weakens the cell's self-defense. With inhibiting PL^{pro} we can also enhance the cell's immune response."

For the experiments, PL^{pro} was mixed with each of the 500 natural substances in a solution, giving them the chance to bind to the enzyme. It is not possible to see if a substance binds to the enzyme with a conventional light microscope. Instead, tiny crystals were grown from the mixtures. When illuminated with the bright X-rays from PETRA III at the experimental station P11, the crystals produced a characteristic diffraction pattern from which the structure of the enzyme can be

reconstructed down to the level of individual atoms. "From this information we can produce 3-dimensional models of the enzyme with atomic resolution and see if and where a substance binds to it," explains Meents.

The screening showed that three phenols bind to the enzyme: hydroxyethylphenol (YRL), isolated for the experiments from the henna tree *Lawsonia alba*, is a compound present in many foods such as red wine and virgin [olive oil](#) and used as anti-arrhythmia agent. Hydroxybenzaldehyde (HBA) is a known anti-tumor agent and accelerates wound healing. It was isolated from the copperleaf *Acalypha torta*. Methyl dihydroxybenzoate (HE9), isolated from the French marigold *Tagetes patula*, is an anti-oxidant with anti-inflammatory effect and is found in green tea.

In subsequent lab tests, established and performed by Hévila Brognaro in Betzel's group, the three phenols reduced PL^{Pro}'s activity by 50–70% in living cells. "The advantage of these substances is their proven safety," says Betzel, who is also a member of the cluster of excellence CUI: Advanced Imaging of Matter. "These compounds naturally occur in many foods. However, drinking green tea will not cure your corona infection. Like it will not heal your wounds or cure your cancer. If and how a corona drug can be developed from these phenols is subject to further studies."



Methylidihydroxybenzoate (HE9) was isolated from the French marigold *Tagetes patula*. Credit: Pixabay, Sonja Kalee

In a different screening, a team consisting largely of the same scientists had already screened thousands of existing drugs at PETRA III as possible inhibitors of the coronavirus' main protease (M^{pro}), also a molecular pair of scissors and a main potential drug target. The screening identified several corona drug candidates, and the most promising have entered preclinical testing. "The corona initiative from DESY and University of Hamburg is one of the very few worldwide that investigated both of COVID-19's main targets," emphasizes Betzel.

More information: Vasundara Srinivasan et al, Antiviral activity of

natural phenolic compounds in complex at an allosteric site of SARS-CoV-2 papain-like protease, *Communications Biology* (2022). DOI: [10.1038/s42003-022-03737-7](https://doi.org/10.1038/s42003-022-03737-7)

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