# Exploring the potential of natural anticoagulants for COVID-19 treatment

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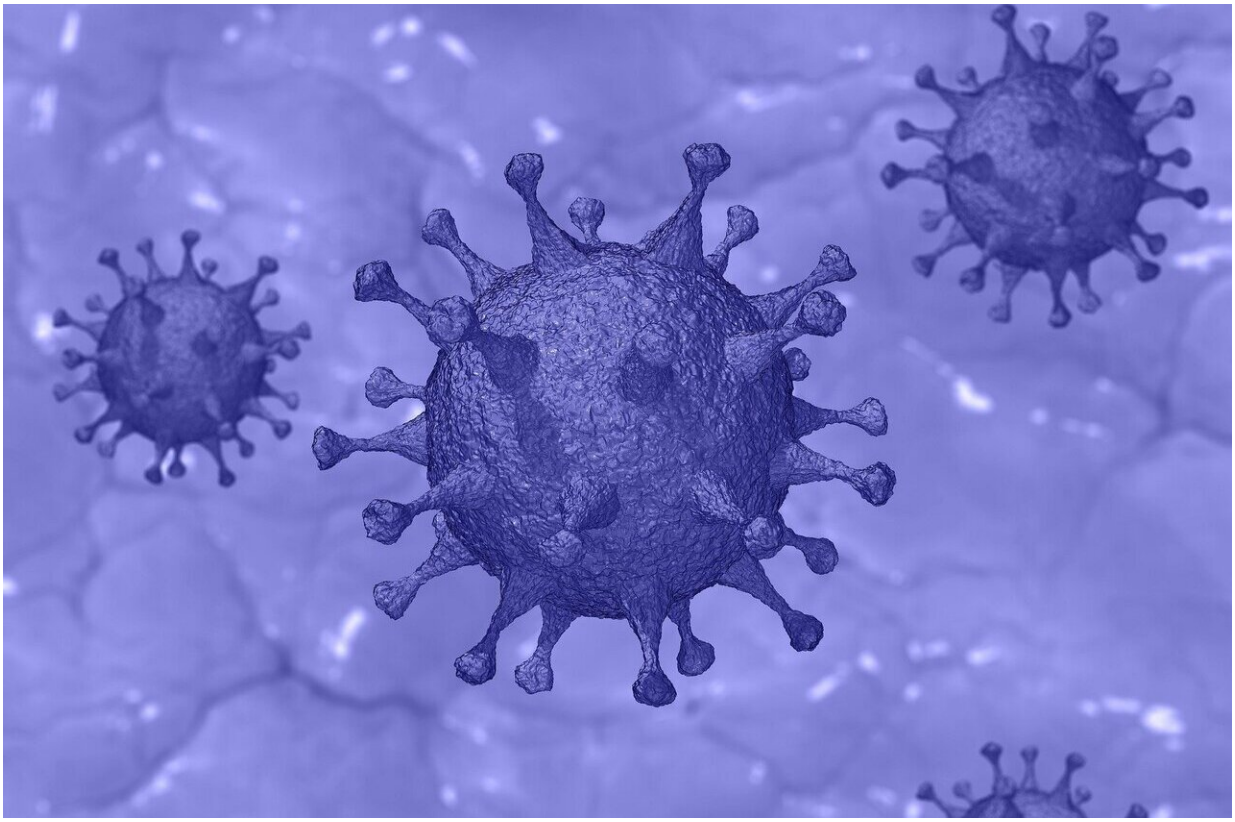

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The treatment of patients with severe COVID-19 following SARS-CoV-2 infection remains difficult. Severe inflammatory reactions and thrombotic complications (blood clots) in particular can be life-

threatening. Classic anticoagulants such as heparin often cannot prevent these complications.

An evaluation of literature data shows that natural anticoagulants, known as plasma protease inhibitors, are important in the regulation of out-of-control inflammatory and coagulation processes and should be reviewed for their therapeutic benefits. The journal *Biologicals* reports on the results online ahead of print.

There is still an urgent need for effective therapeutics for the treatment of severe COVID-19. One approach that has been discussed is passive immunization via transfusion of COVID-19 convalescent plasma (CCP). Despite intensive studies, no clear evidence for the efficacy of CCP has been provided thus far, which could be due to differences in study parameters.

However, a new study showed mortality decreased significantly after administration of CCP with a high antibody titer within five days of the start of invasive ventilation. Questions still remain about the effectiveness of CCP and manufactured COVID-19 hyperimmune globulin (CHIG). Other recent studies have so far found little to no effect on total mortality.

Professor Rainer Seitz was a clinician at the University Hospital of Marburg and head of the Hematology and Transfusion Medicine Division at the Paul-Ehrlich-Institut. He investigated this topic with two fellow retired colleagues: Professor Lutz Gürtler, former virologist at the Ludwig-Maximilians-Universität München (LMU) and Professor Wolfgang Schramm, former hematologist at LMU. They evaluated the available data on the three natural protease inhibitors antithrombin III (ATIII), α1-antitrypsin (α1-AT) and α2-macroglobulin (α2-M). Protease inhibitors inhibit the activity of protein-degrading enzymes.

Protease Inhibitor antithrombin III (ATIII) is available as a plasma-derived concentrate and is found at significantly reduced levels in severe COVID-19 cases. This suggests that ATIII is gradually consumed and its supplementation may be an option, particularly as ATIII has been shown to inhibit the activity of transmembrane serine protease 2 (TMPRSS2). Clinical studies have shown that ATIII plasma levels are significantly lower in individuals who have not survived infection than in survivors.

Protease inhibitor α1-antitrypsin (α1-AT) is approved to treat adults with severe α1-AT deficiency to slow the progression of emphysema (damage to pulmonary alveoli). Epidemiological studies found a correlation between α1-AT deficiency and COVID-19 pathogenesis. α1-AT also inhibits TMPRSS2 activity and thus could be therapeutically relevant.

The protease inhibitor α2-macroglobulin (α2-M) is currently not available as a therapeutic preparation. Clinical data indicate a reduction in α2-M in COVID-19 patients. There are several arguments in favor of further exploring its predictive and therapeutic potential, as it is a versatile facilitator of host defense systems.

In conclusion, the authors emphasize that they consider intensive research necessary to further explore the promising possibilities of plasma protease inhibitors in COVID-19 therapy. From their point of view, this research could not only improve the prognosis of COVID-19 patients, but also open up new therapeutic fields for other diseases such as sepsis—the most severe form of infection, also known as blood poisoning.

**More information:** Rainer Seitz et al, COVID-19: A case for plasma derived natural anticoagulants?, *Biologicals* (2024). DOI: 10.1016/j.biologicals.2024.101781

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