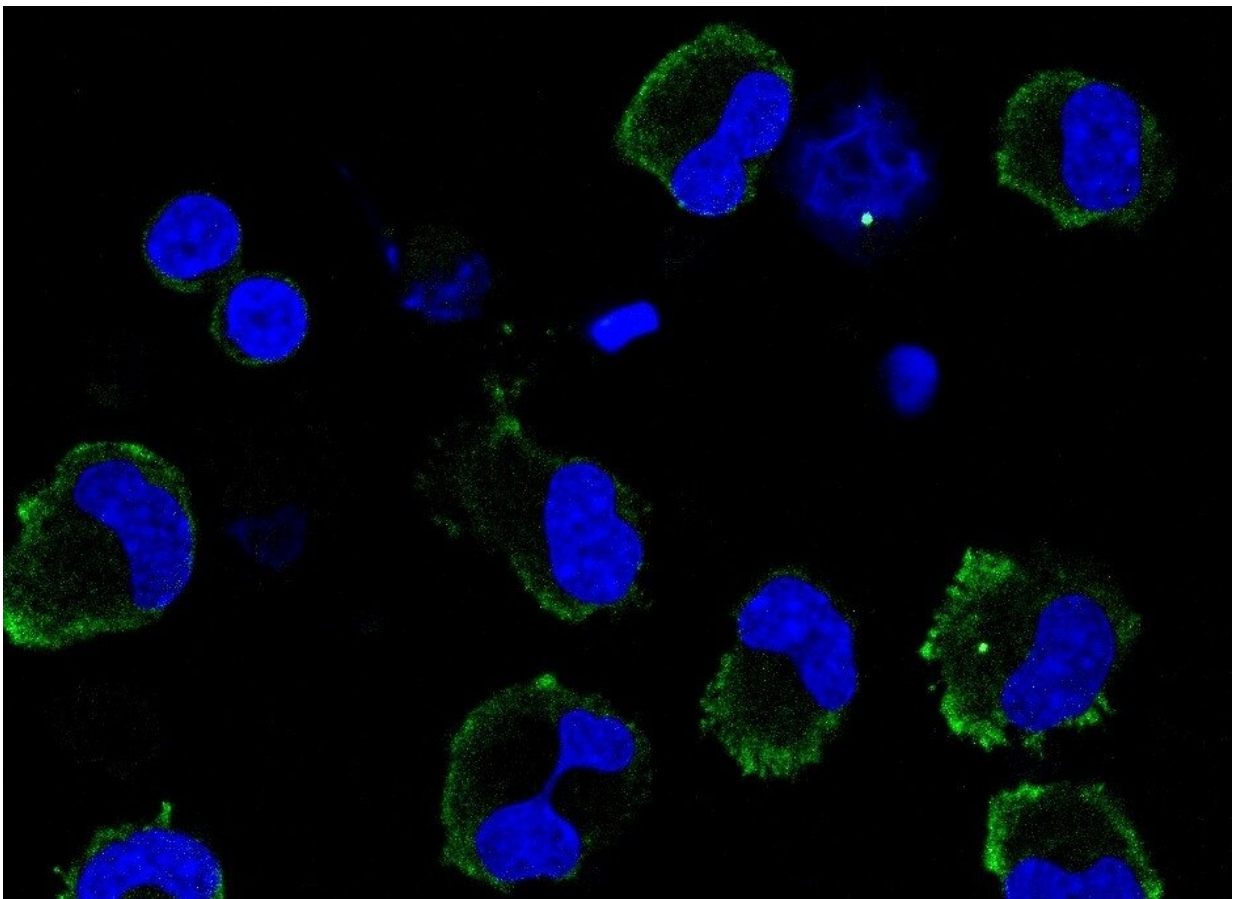


# In pre-clinical trials, drug shows potential to combat exaggerated inflammation associated with COVID-19

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Immunofluorescence of inflammasomes in macrophages infected by SARS-CoV-2. The protein ASC, which is involved in inflammasomes, is stained green. Macrophage nuclei are stained blue. Credit: Leticia Almeida & Keyla Sá/USP

Experiments involving animals and human cells conducted at the University of São Paulo (USP) in Brazil suggest that niclosamide, an anthelmintic widely used against tapeworms, effectively inhibits SARS-CoV-2 replication as well as the exacerbated inflammatory response that leads to death in many patients with severe COVID-19.

More research is needed to find out whether the effects, described in an article published in *Science Advances*, are confirmed in patients with the disease, and according to the authors this will require the development of a novel formulation of the [drug](#), as the one currently available from pharmacies is orally administered and would not affect the lungs.

"The commercially available niclosamide pills aren't absorbed by the stomach and therefore act against intestinal worms. They won't be any use to combat COVID-19 if taken orally. To surmount this problem, it will be necessary to develop a formulation that delivers the drug directly to the lungs," said Dario Zamboni, last author of the article.

Zamboni is a professor at the Ribeirão Preto Medical School (FMRP-USP) and affiliated with the Center for Research on Inflammatory Diseases (CRID).

According to Zamboni, the anti-inflammatory effects of niclosamide observed in the study were due to inhibition of an immune system mechanism known as the [inflammasome](#), a protein complex present in the interior of defense cells. When this [cellular machinery](#) is activated, pro-inflammatory molecules called cytokines are produced to warn the [immune system](#) that more defense cells need to be sent to the site of the infection.

Previous research by the FMRP-USP group showed that inflammasomes in severe COVID-19 patients are typically more activated than normal and remain so even after the virus has been eliminated from the

organism, causing an exaggerated systemic inflammatory response known as a cytokine storm that injures the lungs and other organs.

Zamboni stressed, however, that niclosamide should not be used prophylactically to prevent exacerbated inflammation. "A little inflammation is important to combat infection by pathogenic microorganisms," he said. "Exaggerated inflammation is the problem, as is often the case in severe COVID-19. We're not recommending prophylactic use of the drug, since this could even hinder a recovery by mild or moderate COVID-19 patients."

## Cell cleansing

Niclosamide has been on the market for many years and is mainly prescribed to treat taeniasis (tapeworm infection). It has recently aroused interest among researchers due to claims of potential antiviral action.

According to the authors of the *Science Advances* article, niclosamide promotes autophagy, a vital process that removes and recycles unwanted or damaged molecules from the body's cells. When this process of autophagic cell cleansing is induced, old organelles are destroyed, cellular components are recycled and inflammasomes are deactivated. The process also inhibits replication of SARS-CoV-2 inside cells.

The researchers began the study by screening 2,560 compounds, many of which are already used in humans, in a search for substances capable of inflammasome modulation. This involved infecting human defense cells in vitro with *Legionella*, a bacterium known for inflammasome activation.

After selecting the three most promising drugs, the researchers tested them on mice infected with SARS-CoV-2 and [white blood cells](#) from COVID-19 patients. They also tested the effects of these drugs on

macrophages and monocytes, front-line immune cells intensely involved in COVID-related inflammasomes. Niclosamide produced the best results.

To investigate its antiviral action, the researchers tested it on monocytes infected in vitro with SARS-CoV-2. "Niclosamide's antiviral action was already known. Indeed, phase 1 [clinical trials](#) involving treatment of COVID-19 patients with the drug are under way right now. Our discovery that it induces autophagy and inhibits inflammasomes offers additional information on the immunomodulatory functions of this highly promising drug," Zamboni said.

## Effects on other diseases

The discovery of an inflammasome-inhibiting drug opens up prospects of novel therapies for other conditions involving inflammation, such as autoimmune and neurodegenerative disorders, flu, some kinds of cancer, and [infectious diseases](#) such as zika, chikungunya and Mayaro fever.

"The study focused on COVID-19, but in theory niclosamide should also promote inflammasome inhibition in these other cases. Our results point to numerous other research possibilities," Zamboni said.

**More information:** Letícia de Almeida et al, Identification of immunomodulatory drugs that inhibit multiple inflammasomes and impair SARS-CoV-2 infection, *Science Advances* (2022). [DOI: 10.1126/sciadv.abo5400](https://doi.org/10.1126/sciadv.abo5400)

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