

# Oxysterols: A New Hope for an Effective and Safe Therapy for COVID-19, another Light at the End of the Tunnel

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## ABSTRACT

The COVID-19 pandemic and its lasting consequences have dealt a huge, irreversible blow to the vitality of the global economy and the livelihood of all populations affected by it. Millions of lives lost, businesses destroyed, hopes and dreams shattered and the pandemic still persists despite the remarkable impact of newly developed vaccines. Unfortunately, there are still many uncertainties that threaten our future:

- Harmful new variants of SARS-CoV-2, the COVID-19 virus, emerging from a constantly mutating virus that may render the existing vaccines less effective or even ineffective.
- The colossal task of vaccinating the entire world population, combined with a likely need for repeat vaccination.
- The side effects of the available vaccines, especially in certain segments of the population, including young men and pregnant or to be pregnant women. Unfortunately, not much is currently known about potential long term side effects of the newly developed vaccines.

**Keywords:** SARS-CoV-2; COVID-19 virus; Vaccines; Oxysterols

## DESCRIPTION

Beyond mass vaccination, there exists a pressing need to develop safe and effective strategies for dealing with this nasty pandemic that could be deployed in the rich and the not so rich countries around the world. Development of inexpensive, safe, and reliable oral medications to fight COVID-19, applicable in prophylactic and outpatient settings, could be helpful in this regard. Existing COVID-19 drugs, like Remdesivir, must be administered through intravenous injection and is only given to individuals with significant disease in a hospital setting.

## OXYSTEROLS TO THE RESCUE

In a recently published peer-reviewed paper, we reported results from studies performed in collaboration with our colleagues at the National Institute of Infectious Diseases (NIID) in Tokyo, Japan [1]. These studies stem from our nearly two-decade old interest in the biological activities of a specific class of molecules called oxysterols [2,3]. Oxysterols are products of cholesterol oxidation and many naturally occurring members of this family have been shown to possess important biological and physiological effects. In fact, anti-viral properties of some naturally occurring

oxysterols, such as 25-hydroxycholesterol (25-OHC), against HIV and SARS-CoV-2 have been reported [4,5]. Unfortunately, most naturally occurring oxysterols do not display favorable pharmacokinetic and drug safety properties that would render them suitable candidates for therapeutic development. With our colleagues in Japan, we were able to screen a library of semi-synthetic oxysterol compounds with more favorable properties, including oral bioavailability, pharmacokinetic, tissue distribution and safety profiles, combined with low cost of production. Our efforts identified at least two potential candidates with robust in vitro anti-viral activity that can inhibit SARS-CoV-2 replication in host cells. Importantly, these oxysterol compounds display a mechanism of action different from that of vaccines or anti-viral agents, like Remdesivir, that directly target the SARS-CoV-2 virus. Instead, the oxysterols act on the host cells and inhibit the ability of the virus to hijack the host cell's machinery that it requires for its replication/propagation. These so-called double membrane vesicles (DMVs) are structures formed in infected host cells that act like factories of SARS-CoV-2 replication [6,7]. Inhibition of DMV formation by oxysterols blocks the ability of the virus to propagate and overwhelm the host's immune system, allowing the host to mount a more effective defense to destroy the virus. By targeting the host cells and not the virus, many of the issues

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and concerns with a mutating virus are lessened or nonexistent. Potentially, oxysterol-based therapies with acceptable drug safety and oral bioavailability could be applied at the first signs of infection, or given to those that may be at a higher risk of getting infected due to comorbidities or exposure to infected individuals.

Our hope is that oxysterol-based therapeutics for Covid-19 could potentially become a much needed game changer in the fight against this devastating disease. We need global populations to reach a true sense of normalcy without the constant fear of yet another deadly wave of SARS-CoV-2 variant, once again putting us through the nightmare that we all just went through for the past 18 months!

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