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FXR inhibition may protect from SARS-CoV-2 infection by reducing ACE2

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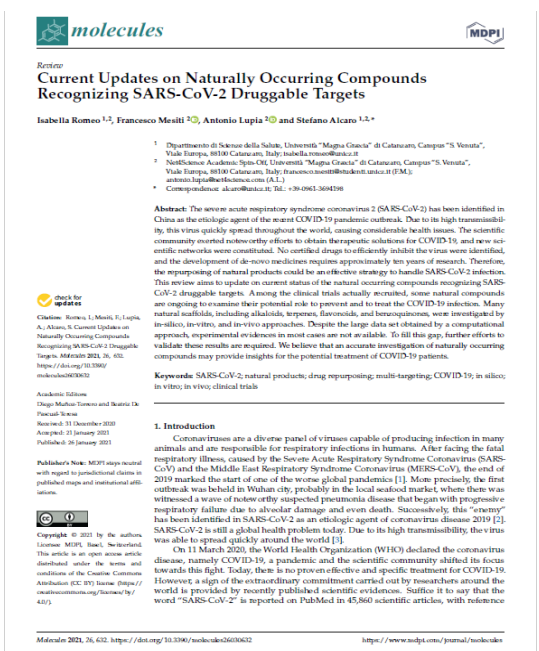
La prevención de la infección por SARS-CoV-2 mediante la modulación de los receptores virales del huésped, como la enzima convertidora de angiotensina 2 (ECA2) , podría representar un nuevo enfoque quimioprofiláctico para COVID-19 complementario a la vacunación.

Se identificó que al bloquear una proteína denominada receptor X farnesoide (FXR) se reduce la cantidad de ECA2 en la superficie celular de diversos tejidos como gastrointestinal y respiratorio.

En este artículo se demostró que con el uso del ácido ursodeoxicólico (AUDC) se redujo la expresión de la ECA2 en células de modelos organoides de pulmón, intestino e hígado, así como en el epitelio nasal humano. La modulación de esta vía podría ser beneficiosa para reducir la infección por SARS-CoV-2, facilitando el camino para futuros ensayos clínicos.



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Review

Current Updates on Naturally Occurring Compounds Recognizing SARS-CoV-2 Druggable Targets

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Abstract: The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been identified in China as the etiologic agent of the recent COVID-19 pandemic outbreak. Due to its high transmissibility, this virus quickly spread throughout the world, causing considerable health issues. The scientific community exerted noteworthy efforts to obtain therapeutic solutions for COVID-19, and new scientific networks were constituted. No certified drugs to efficiently inhibit the virus were identified, and the development of de-novo medicines requires approximately ten years of research. Therefore, the repurposing of natural products could be an effective strategy to handle SARS-CoV-2 infection. This review aims to update on current status of the natural occurring compounds recognizing SARS-CoV-2 druggable targets. Among the clinical trials actually recruited, some natural compounds are ongoing to examine their potential role to prevent and to treat the COVID-19 infection. Many natural scaffolds, including alkaloids, terpenes, flavonoids, and benzoquinones, were investigated by in-silico, in-vitro, and in-vivo approaches. Despite the large data set obtained by a computational approach, experimental evidences in most cases are not available. To fill this gap, further efforts to validate these results are required. We believe that an accurate investigation of naturally occurring compounds may provide insights for the potential treatment of COVID-19 patients.

Keywords: SARS-CoV-2; natural products; drug repurposing; multi-targeting; COVID-19; in silico; in vitro; in vivo; clinical trials

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1. Introduction

Coronaviruses are a diverse panel of viruses capable of producing infection in many animals and are responsible for respiratory infections in humans. After facing the fatal respiratory illness, caused by the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), the end of 2019 marked the start of one of the worse global pandemics [1]. More precisely, the first outbreak was beheld in Wuhan city, probably in the local seafood market, where there was witnessed a wave of noteworthy suspected pneumonia disease that began with progressive respiratory failure due to alveolar damage and even death. Successively, this "enemy" has been identified in SARS-CoV-2 as an etiologic agent of coronavirus disease 2019 [2]. SARS-CoV-2 is still a global health problem today. Due to its high transmissibility, the virus was able to spread quickly around the world [3].

On 11 March 2020, the World Health Organization (WHO) declared the coronavirus disease, namely COVID-19, a pandemic and the scientific community shifted its focus towards this fight. Today, there is no proven effective and specific treatment for COVID-19. However, a sign of the extraordinary commitment carried out by researchers around the world is provided by recently published scientific evidences. Suffice it to say that the word "SARS-CoV-2" is reported on PubMed in 45,860 scientific articles, with reference

Romeo, I., Mesiti, F., Lupia, A., & Alcaro, S. (2021). Current updates on naturally occurring compounds recognizing SARS-CoV-2 druggable targets. Molecules, 26(3), 632.

En esta revisión se verificó el estado actual de los compuestos naturales que tiene como objetivo farmacológico prevenir y tratar la infección por COVID-19.

El cribado en vitro y resultado *in silico,* confirmaron que el ácido ursodeoxicólico y su conjugado de taurina ejercen una actividad inhibidora frente al receptor de la ECA2, sin embargo, se requieren mayores estudios clínicos para confirmar esta actividad biológica.

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Viewpoint

Merit of an Ursodeoxycholic Acid Clinical Trial in COVID-19 Patients

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Abstract Corona Virus Disease 2019 (COVID-19) has affected over 8 million people worldwide. We underscore the potential benefits of conducting a randomized open-label unblinded clinical trial to evaluate the role of ursodeoxycholic acid (UDCA) in the treatment of COVID-19. Some COVID-19 patients are characterized with cytokine storm syndrome that can cause severe and irreversible damage to organs leading to multi-organ failure and death. Therefore, it is critical to control both programmed cell death (apoptosis) and the hyper-immune inflammatory response in COVID-19 patients to reduce the rising morbidity and mortality. UDCA is an existing drug with proven safety profiles that can reduce inflammation and prevent cell death. *National Geographic* reported that, "China Promotes Bear Bile as Coronavirus Treatment". Bear bile is rich in UDCA, comprising up to 40–50% of the total bile acid. UDCA is a logical and attainable replacement for bear bile that is available in pill form and merits clinical trial consideration.

Keywords: Coronavirus; COVID-19; cytokine storm; ursodeoxycholic acid; clinical trial

Coronavirus SARS-CoV-2 as the cause of COVID-19 (Corona Virus Disease 2019) has affected over 8 million people worldwide. One of the consensus observations emerging among COVID-19 patients is the systemic inflammation associated with disease severity [1]. There is mounting evidence showing that some COVID-19 patients are presenting with a cytokine storm syndrome similar to secondary hemophagocytic lymphohistiocytosis (sHLH) and is associated with the degree of disease severity [2]. Studies comparing overlapping clinical features and pathogenesis of COVID-19 and sHLH have shown overlapping markers of inflammation [3]. Therefore, treatment with antiviral drugs alone may not be sufficient to combat COVID-19 related cytokine storm syndrome. Several anti-inflammatory agents have been considered to reduce inflammation in COVID-19 patients [4]. Those infected with SARS-CoV-2 show a significant increase in cytokine profiles such as IL-2, IL-17, and TGFα [5,6]. In the early stages of infection, $CD4^+$ and $CD8^+$ T cells are critical for defense against SARS-CoV-2. $CD4^+$ T cells induce virus-specific antibodies by stimulating B cells. On the other hand, $CD8^+$ T cells attack and kill the viral infected cells. To support the immune system, proinflammatory cytokines are produced by helper T cells. However, the increasing viral load can induce apoptosis of T cells, leading to an increased immune response in the patient [7]. The overreaction of inflammatory cytokines, or hyper-inflammatory syndrome, can cause severe and irreversible damages to the lungs and other organs leading to cell death and multi-organ system failure.

Therefore, it is critical to control both apoptosis and the hyper-immune inflammatory response in COVID-19 patients to reduce the rising morbidity and mortality. While reducing hyper-inflammation may be helpful in COVID-19 patients, overall immune suppression using corticosteroids may lead to delayed virus clearance and enhance mucus and impaired antimicrobial peptide secretion [8].

Subramanian, S., Iles, T., Ikramuddin, S., & Steer, C. J. (2020). Merit of an ursodeoxycholic acid clinical trial in COVID-19 patients. *Vaccines*, *8*(2), 320.

Algunos pacientes con COVID-19 se caracterizan por presentar tormenta de citosinas, la cual puede causar daños graves e irreversibles en los órganos y conducir a un fallo multiorgánico y a la muerte. Por lo tanto, es fundamental controlar tanto la muerte celular programada (apoptosis), como la respuesta inflamatoria hiperinmune en los pacientes con COVID-19 para reducir el aumento de la morbilidad y la mortalidad.

Un estudio reciente ha demostrado que los metabolitos de los ácidos biliares regulan la diferenciación de linfocitos T *helper,* T reguladores y controlan la homeostasis inmunológica. Los ácidos biliares también controlan la inflamación, en parte mediante la inhibición de NLRP3.

El ácido ursodesoxicólico (AUDC), es un fármaco con perfiles de seguridad probados que puede prevenir la muerte celular y reduce significativamente las citoquinas proinflamatorias como TNF, IL-1, IL 2 e IL-6.