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RESEARCH HIGHLIGHTS

Development of a Novel Anti-SARS-CoV-2 Antiviral: Effective Inhibitory Activity of Brilacidin

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The race to develop effective therapeutics/therapies against SARS-CoV-2 infections and COVID-19 is ongoing as the pandemic is still far from being controlled. Recently, three groups of scientists including Bakovic, et al. [1], Xu, et al. [2]and Hu, et al. [3] respectively, reported a promising and highly attractive antiviral activity of a new drug, named brilacidin, against SARS-CoV-2 infections. Briefly, they discovered that brilacidin, a *de novo* mimetic of Host Defense Peptides (HDPs), efficiently protects cells from infections by several strains of SARS-CoV-2 including wild type and Variant of Concern (VOCs) strains, specifically through both a viral inactivation and a blocking of interaction of SARS-CoV-2 proteins with host cell surface Heparan Sulfate Proteoglycans (HSPGs).

Since the end of the year 2019, the worldwide economy has drastically dropped [4] as the lifestyle population across the world has strictly been reduced to a stay-at-home policy, to break the transmission line of the deadly breakout caused by the new Coronavirus Disease (COVID-19). Declared pandemic in March 11, 2020 [5], COVID-19, caused by the severe Acute Respiratory Syndrome-Associated Coronavirus 2 (SARS-CoV-2) [6] has killed around 6,343,571 people worldwide by June 22, 2022. The strict compliance with the stay-at-home policy [7] and the use of other strategies, including administration of immunized plasma from recovered COVID-19 patients (known as Convalescent Plasma (CP)) [8] and drug repositioning [9], has reduced the spread of SARS-CoV-2, while developing specific antiviral treatments, including drugs and vaccines. However, the emergence of new SARS-CoV-2 variants has rendered the epidemiological fight more challenging as these emerging SARS-CoV-2 variants are more infectious and severe, escape the immune response, and resist to the treatments used against the originate SARS-CoV-2 [10,11]. Thus, today, the COVID-19-caused health crisis is still uncontrolled in many part of the world.

Right after the health crisis outbreak, the first FDA- and WHO-recommended treatment adopted to contain COVID-19 threat was based on drug repositioning/repurposing approach. This approach includes the use of drugs initially developed for specific disease treatments other than COVID-19. The main drugs used to treat COVID-19 patients include Chloroquine and Hydroxychloroquine, dexamethasone, Umifenovir, Ivermectin, Lopinavir-Ritonavir, and Remdesivir. However, it was quickly discovered that these drugs was associated with important side effects, with critical negatives effects on health (occurrence of illness and organ damage) (Table 1), which lead to a stop-of-use of certain drugs [9,12,13].

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In the need of reinforcing the drug repositioning strategy and developing specific SARS-CoV-2 treatment, recently, three main groups of scientists discovered that a new antibacterial drug, named brilacidin, provides attractive benefits against SARS-CoV-2, and specifically without major side effects [1-3]. First, early in 2021, Bakovic, et al. [1] demonstrated with strong evidence that brilacidin hampers the entry of SARS-CoV-2 into Calu3 and Vero cells, used as infection models, by interacting in with both the virus and cells. Specifically, pretreated with 10 uM of brilacidin (a well-tolerated concentration by mammal cells), Calu3 and Vero cells were protected from SARS-CoV-2 infection after a significant long virus exposure time of 16 to 24 hours. This suggested that brilacidin interacts directly with cells, then block entry of SARS-CoV-2. Moreover, not only was it found that brilacidin could prevent SARS-CoV-2 entry by interacting with cell surface compounds, but also brilacidin could disrupt the SARS-CoV-2 integrity blocking the viral replication, which prevents the viral infection; this was characterized by a crucial low viral load after pretreatment of viral inoculum, but not cells. Remarkably, the inhibition/protection effect of brilacidin was drastically enhanced (up to 95%), along with a decreased of SARS-CoV-2 titer (of 33%) when virus inoculum was brilacidin-based pretreated compared to when cells were pretreated. This suggests that brilacidin interacts more with SARS-CoV-2 compounds than with that of the host cells (Figure 1), and could achieve a 90% protection against SARS-CoV-2 infection with a low and human body tolerable drug concentration of 2.63 uM. Combined with Remdesivir, a proven anti-SARS-CoV-2 antiviral (2.5 uM each), this inhibition/protection effect was increased and sustained to more than 99%, with a cell viability of more than 95%.

Table 1: Revealed side effects associated with the main drugs used to treat COVID-19 patients.

Drugs	Initial approved treatment	Associated side effects in COVID-19 patients
Azithromycin	Antibacterial and antibiotic	Diarrhea, nausea, abdominal pain, and vomiting, allergic reactions such as anaphylaxis, QT prolongation, or Clostridium difficile infection [12,13]
Chloroquine and Hydroxychloroquine	Anti-malarial, anti-chronic inflammatory diseases.	cardiovascular issues (QT prolongation with fatal arrhythmias), liver or kidney damage, retinopathy, and hypoglycemia [9,12]
Dexamethasone	Anti-inflammatory conditions (e.g., bronchial asthma, endocrine and rheumatic disorders).	gastritis, vomiting, headache, dizziness, insomnia, restlessness, depression, acne, irregular or absent menstrual periods [12]
Ivermectin	Anti-parasitic (intestinal strongyloidiasis and onchocerciasis, pediculosis and rosacea)	Required high dose against COVID-19 induces side effects in patients [9]
Lopinavir/Ritonavir	Anti-HIV	Lack of vital benefits for COVID-19 patients [9]
Ribavirin		Osteoarthritis, arthritis, bronchitis [12,13]
Remdesivir	Anti-Ebola virus	Hepatocellular toxicity, nausea, anemia, kidney injury, hypotension, respiratory failure, and constipation [9,12]
Umifenovir	Anti-Influenza and anti-respiratory viruses.	Lack of vital benefits for COVID-19 patients [9]

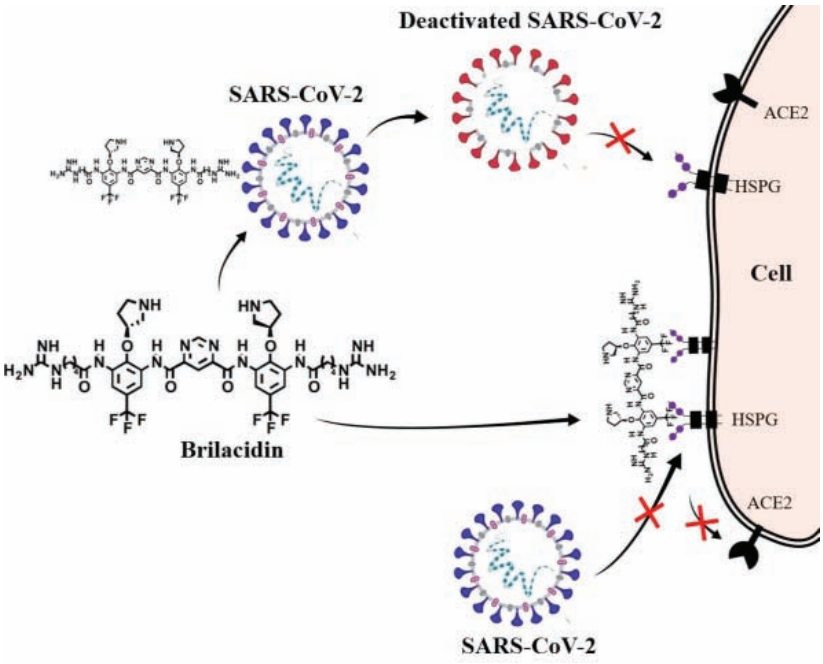

Figure 1 Antiviral mechanisms of Brilacidin.
Brilacidin can inhibit SARS-CoV-2 entry into cells through interaction with both host cell surface HSPG and SARS-CoV-2 proteins to block viral attachment deactivate viral particles.

This previous findings were confirmed by Xu, et al. [2], who further, specified that the protective effect of brilacidin is more likely to be preventive than curative, as brilacidin has no inhibition/protective effect after SARS-CoV-2-cell attachment, but only can inhibit SARS-CoV-2 entry into cells. Specifically, they demonstrated that when cell are pretreated before with brilacidin, brilacidin directly interacts with cell surface glycosaminoglycans, such as heparan sulfate which hamper the first steps of viral infection, and that this mechanism is not possible once SARS-CoV-2 is already attached. This inhibition mechanism has later been supported by Hu, et al. [3], who described that brilacidin targets Heparan Sulfate Proteoglycans (HSPGs) on the host cell surface and inhibits SARS-CoV-2 entry into cells. Also, Xu et al. [2] described that the pretreatment of viral inoculum resulted in viral aggregation of brilacidin, and more likely its saturation onto membrane or nucleocapside proteins [14], but not spike protein, then preventing infection. This suggested that brilacidin inhibits SARS-CoV-2-host cell binding through a mechanism independent from direct spike-ACE2 complex disruption (Figure 1).

Furthermore, while Xu, et al. [2] demonstrated the effectiveness of brilacidin against SARS-CoV-2 and its derivative variants including P.1 and B.1.1.7 strains, Hu, et al. [3] discovered that brilacidin protective activity has a broader spectrum to other sarbecoviruses, including OC43, 229E, and NL63 strains.

To sum up, these three studies demonstrated that brilacidin, a potent antibacterial synthetic HDP mimetic efficiently prevents SARS-CoV-2 entry into cells through interaction with both host cell surface HSPG and SARS-CoV-2 N or M proteins to block viral attachment deactivate viral particles, respectively, and its antiviral activity is broaden to SARS-CoV-2 variants and other HCoVs. This broad-spectrum dual antiviral mechanism of action, which is enhanced when combined with Remdesivir, could break the transmission chain of SARS-CoV-2 and reduce emergence of SARS-CoV-2 resistant variant development. As already in clinical trial for COVID-19 treatment (NCT04784897), supplementary studies are suggested to evaluate safety of the treatment and combination.

Highlights

1. Brilacidin protects cells from SARS-Co-2 infection, at low dose.
2. Brilacidin has a broad-spectrum antiviral activity against multiple Human Coronaviruses (HCoVs) including SARS-CoV-2 and its derivatives, HCoV-229E, HCoV-OC43, and HCoV-NL63.
3. Brilacidin has a dual antiviral mechanism of action, including virucidal activity and binding to coronavirus attachment factor HSPGs on the host cell surface
4. Brilacidin antiviral activity is synergetically enhanced when combined with Remdesevir.

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