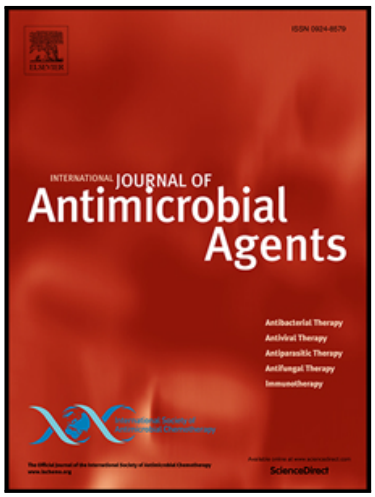
Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.



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Hanan Polansky , Gillad Lori

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Coronavirus (COVID-19), First Indication of Efficacy of Gene-Eden-VIR/Novirin in SARS-CoV-2 Infections

Hanan Polansky[1], (corresponding author), Gillad Lori[1]

[1]The Center for the Biology of Chronic Disease (CBCD)

616 Corporate Way, Suite 2-3665, Valley Cottage, NY 10989

607-256-6070

hpolansky@cbcd.net

gillad@cbcd.net

Running title: *COVID-19, Gene-Eden-VIR, Novirin*

Sir,

The novel coronavirus (COVID-19) outbreak imposes a significant threat to global health with an estimated R_0 of 2.24-4.08 and fatality rate of 3.4%. Samples collected from COVID-19 patients revealed that the novel virus is a betacoronavirus, closely related to the human Severe Acute Respiratory Syndrome (SARS-CoV) with 79.5% sequence identity[1]. In addition, SARS-CoV and COVID-19 have an almost identical 3-Chymotrypsine-Like protease (3CLpro) amino acid sequences, with 96% identity and 99% similarity[2]. To expedite the development of new treatments, several existing drugs, which were found effective against RNA viruses and particularly against SARS, are currently tested for their effect on the COVID-19 virus.

Gene-Eden-VIR/Novirin is a patented herbal broad-spectrum antiviral treatment. Its formula includes five ingredients: a 100 mg extract of quercetin, a 150 mg extract of green tea, a 50 mg extract of cinnamon, a 25 mg extract of licorice, and 100 μg of selenium. Clinical trials showed that Gene-Eden-VIR/Novirin is effective against several viruses, including the Human Papillomavirus (HPV)[3], Herpes Simplex Virus[4] (HSV), Epstein-Barr virus (EBV), and human Cytomegalovirus (hCMV). In the next section, we review evidence on the effect of the Gene-Eden-VIR/Novirin five ingredients on betacoronaviruses, and specifically, the SARS-CoV virus.

Quercetin and the active ingredients in green tea, called catechins, are polyphenols known as flavonoids. They have a variety of anti-inflammatory, anti-oxidant and anti-enzymatic activities. Quercetin and its derivatives as well as different catechins found in green tea were found to inhibit the SARS proteases[5]. Specifically, Thi Nguyen et al. Found that both Epigallocatechin Gallate and Quecertin inhibit the SARS main protease, 3CLpro with an IC_{50}

of 73uM in vitro. In addition, Ji Young Park et al. reported that Quercetin inhibits both the SARS Proteases, 3CLpro and PLpro, and the Middle Eastern Respiratory Syndrome virus (MERS) 3CLpro protease with an IC_{50} of 52.7uM, 8.6uM and 34.8uM respectively, in vitro[6]. Quecertin also modulates the cellular unfolded protein response (UPR). As coronaviruses can utilize the UPR to complete different stages of the viral life cycle during infection, Nabirotchkin et al. suggested that quercetin may have anti-coronavirus effects through its modulation of this pathway[7].

Cinnamon extract has anti RNA viral effects[8]. Min Zuang et al. showed that the extract inhibited wild type SARS infection *in vitro* with an IC_{50} of 43uM. The proposed possible mechanism was blocking cell entry via endocytosis.

Licorice extract, derived from the root of Glycyrrhiza Glabra, has both broad antiviral and immunostimulating effects[9]. The plant was also reported to have specific anti-SARS effects. Brush et al. demonstrated that the herb stimulates the proliferation and activation of lymphocytes in human subjects. This can be of major importance in the coronavirus infections, since immunocompromised patients may be particularly at risk.

Selenium (Se) is an important trace element in redox regulation. Its antioxidative function is exerted via its incorporation, in the form of selenocysteine, into a group of proteins called selenoproteins[10]. Se deficiency leads to increased levels of reactive oxygen species (ROS) and oxidative stress, and results in a decreased response of the immune system to viruses, and an increased rate of mutation of RNA viruses. The combination of an increase in viral rate of mutation with a decrease in the immune response, has been linked to increased virulence, as it may give rise to a larger population of quasispecies, of which new, more pathogenic

quasispecies may emerge. M. Harthill[11] suggested that this mechanism, which has been observed for other RNA viruses in Se deficient mice models, also occurred in the SARS-CoV outbreak, which emerged in areas of low Se soil in China, such as Wuhan city. Studies showed that Se supplementation to Se deficient patients increased the immune response to viral infections, and decreased the virulence of several viruses, in some cases to the point of complete prevention of the disease[10].

In summary, in this paper we described the effects of Gene-Eden-VIR/Novirin ingredients on betacoronaviruses, and specifically SARS-CoV. We chose SARS-CoV because of its high level of sequence identity to COVID-19. We showed that Gene-Eden-VIR/Novirin ingredients exert a variety of antiviral effects on betacoronaviruses, and SARS-CoV, including inhibition of cell entry and infection, inhibition of replication, inhibition of the viral proteases, enhancing the antiviral immune response, and reducing virulent quasispecies formation. We regard the evidence presented in this paper as first indication of efficacy. Next, we are planning to collect clinical data on the effect of Gene-Eden-VIR/Novirin on the SARS-CoV-2 virus from users of the treatments. We will use this clinical data to further our understanding of the effects of the treatments on individuals at risk and those infected with the virus.

Declarations

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Competing Interests: Hanan Polansky is the inventor of the Gene-Eden-VIR/Novirin formula. Gillad Lori has no conflict of interest.

Ethical Approval: Not required

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