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.

International Journal of Antimicrobial Agents 55 (2020) 105971

Contents lists available at ScienceDirect

International Journal of Antimicrobial Agents

journal homepage: www.elsevier.com/locate/ijantimicag

Letter to the Editor

Coronavirus disease 2019 (COVID-19): first indication of efficacy of Gene-Eden-VIR/Novirin in SARS-CoV-2 infection

Sir,

The outbreak of coronavirus disease 2019 (COVID-19) caused by a novel coronavirus represents a significant threat to global health, with an estimated R_0 of 2.24–4.08 and a 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 coronavirus (SARS-CoV) with 79.5% sequence identity [1], and the novel coronavirus has been named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Moreover, SARS-CoV and SARS-CoV-2 have almost identical 3-chymotrypsine-like protease (3CLpro) amino acid sequences, with 96% identity and 99% similarity [2]. To expedite the development of new treatments for COVID-19, several existing drugs that were found to be effective against RNA viruses, and particularly against SARS-CoV, are currently being tested for their efficacy against SARS-CoV-2.

Gene-Eden-VIR/Novirin is a patented herbal broad-spectrum antiviral treatment. Its formula includes five ingredients, comprising a 100 mg extract of quercetin, a 150 mg extract of green tea, a 50 mg extract of cinnamon, a 25 mg extract of liquorice and 100 µg of selenium. Clinical trials have shown that Gene-Eden-VIR/Novirin is effective against several viruses including human papillomavirus [3], herpes simplex virus [4], Epstein–Barr virus and human cytomegalovirus. Here we review the evidence on the effect of the five ingredients in Gene-Eden-VIR/Novirin 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 various catechins found in green tea were found to inhibit the SARS-CoV proteases [5]. Specifically, Nguyen et al. found that both epigallocatechin gallate and quercetin inhibit the SARS-CoV main protease (3CLpro) with an IC_{50} (50% inhibitory concentration) in vitro of 73 µM [5]. In addition, Park et al. reported that quercetin inhibits in vitro both of the SARS-CoV proteases (3CLpro and PLpro) as well as the Middle Eastern Respiratory Syndrome coronavirus (MERS-CoV) 3CLpro protease with IC_{50} values of 52.7, 8.6 and 34.8 µM respectively [6]. Quercetin also modulates the cellular unfolded protein response (UPR). As coronaviruses can utilise 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 antiviral effects against RNA viruses. Zuang et al. showed that cinnamon extract inhibited wild-type SARS-CoV in vitro with an IC_{50} of 43 µM [8]. The possible proposed mechanism of action was by blocking cell entry via endocytosis.

Liquorice 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 [9]. This can be of major importance in 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]. Selenium deficiency leads to increased levels of reactive oxygen species (ROS) and oxidative stress, and results in a decreased immune response to viruses and an increased rate of mutation of RNA viruses. The combination of an increase in viral mutation rate and a decrease in the immune response has been linked to increased virulence as it may give rise to a larger population of quasispecies, from which new more pathogenic quasispecies may emerge. Harthill suggested that this mechanism, which has been observed for other RNA viruses in selenium-deficient mice models, also occurred in the SARS-CoV outbreak, which emerged in areas of low-selenium soil in China, such as Wuhan city [11]. Studies showed that selenium supplementation to selenium-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, here we describe the effects of Gene-Eden-VIR/Novirin ingredients on Betacoronaviruses, specifically SARS-CoV. We chose SARS-CoV because of its high level of sequence identity to SARS-CoV-2, the causative agent of COVID-19. We showed that the ingredients of Gene-Eden-VIR/Novirin exert a variety of antiviral effects on Betacoronaviruses and SARS-CoV, including inhibition of cell entry and infection, inhibition of replication, inhibition of viral proteases, enhancing the antiviral immune response, and reducing virulent quasispecies formation. We regard the evidence presented as a first indication of efficacy. Next we are planning to collect clinical data on the effect of Gene-Eden-VIR/Novirin on SARS-CoV-2 from users of the treatments. We will use these clinical data to further our understanding of the effects of the treatments on individuals at risk and those infected with the virus.

Funding

None.

Ethical approval

Not required.

https://doi.org/10.1016/j.ijantimicag.2020.105971

Declaration of Competing Interest

HP is the inventor of the Gene-Eden-VIR/Novirin formula. GL declares no competing interests.

References

[1] Lu R, Zhao X, Li J, Niu P, Yang B, Wu H, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020;395:391–3. doi:10.1016/S0140-6736(20)30251-8.

[2] Stoermer M. Homology models of coronavirus 2019-nCoV 3CLpro protease. ChemRxiv 2020 Feb 5. doi:10.26434/chemrxiv.11637294.v3.

[3] Polansky H, Itzkovitz E, Javaherian A. Human papillomavirus (HPV): systemic treatment with Gene-Eden-VIR/Novirin safely and effectively clears virus. Drug Des Devel Ther 2017;11:575–83. doi:10.2147/DDDT.S123340.

[4] Polansky H, Javaherian A, Itzkovitz E. Clinical trial of herbal treatment Gene-Eden-VIR/Novirin in oral herpes. J Evid Based Integr Med 2018;23:2515690X18806269. doi:10.1177/2515690X18806269.

[5] Nguyen TT, Woo HJ, Kang HK, Nguyen VD, Kim YM, Kim DW, et al. Flavonoid-mediated inhibition of SARS coronavirus 3C-like protease expressed in *Pichia pastoris*. Biotechnol Lett 2012;34:831–8. doi:10.1007/s10529-011-0845-8.

[6] Park JY, Yuk HJ, Ryu HW, Lim SH, Kim KS, Park KH, et al. Evaluation of polyphenols from *Broussonetia papyrifera* as coronavirus protease inhibitors. J Enzyme Inhib Med Chem 2017;32:504–15. doi:10.1080/14756366.2016.1265519.

[7] Nabirotchkin S, Peluffo A, Bouaziz J, Cohen D. Focusing on the unfolded protein response and autophagy related pathways to reposition common approved drugs against COVID-19. Preprints 2020:2020030302. doi:10.20944/preprints202003.0302.v1.

[8] Zhuang M, Jiang H, Suzuki Y, Li X, Xiao P, Tanaka T, et al. Procyanidins and butanol extract of *Cinnamomi cortex* inhibit SARS-CoV infection. Antiviral Res 2009;82:73–81. doi:10.1016/j.antiviral.2009.02.001.

[9] Brush J, Mendenhall E, Guggenheim A, Chan T, Connelly E, Soumyanath A, et al. The effect of *Echinacea purpurea, Astragalus membranaceus* and *Glycyrrhiza glabra* on CD69 expression and immune cell activation in humans. Phytother Res 2006;20:687–95. doi:10.1002/ptr.1938.

[10] Guillin O, Vindry C, Ohlmann T, Chavatte L. Selenium, selenoproteins and viral infection. Nutrients 2019;11:E2101. doi:10.3390/nu11092101.

[11] Harthill M. Review: Micronutrient selenium deficiency influences evolution of some viral infectious diseases. Biol Trace Elem Res 2011;143:1325–36. doi:10.1007/s12011-011-8977-1.

Hanan Polansky*
Gillad Lori
The Center for the Biology of Chronic Disease (CBCD), 616 Corporate Way, Suite 2-3665, Valley Cottage, NY 10989, USA
*Corresponding author. Tel.: +1 607 256 6070.
E-mail address: hpolansky@cbcd.net (H. Polansky)