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Commentary

Antivirals Against SARS-CoV2: Relevance to the Treatment of Alzheimer's Disease

Ruth F. Itzhaki*
Institute of Population Ageing, University of Oxford, Oxford, UK

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Abstract. A recent study *in vitro* has shown that a sulphated polysaccharide, a type of fucoidan, has potent antiviral activity against SARS-Cov2. If the antiviral action were successful also for COVID-19 patients, it would be enormously valuable against not only acute disease but also long-term mental effects, which might include Alzheimer's disease (AD). In a trial of AD patients, the apparent success of treatment with a polysaccharide, GV971, was suggested to result from antiviral action against herpes simplex virus type 1 (HSV1) in brain, a pathogen strongly implicated in AD, and that sulphation of GV971, making it fucoidan-like, might increase its putative antiviral action. These data indicate that treatment of AD patients might be very effective using valacyclovir, a conventional antiviral, which inhibits viral replication, together with a fucoidan, which blocks virus entry into cells.

Keywords: Alzheimer's disease, antiviral, COVID-19, fucoidans, Herpes simplex virus type 1, SARS-Cov2

The study by Kwon et al. (2020) [1] is potentially very important in showing that complex sulphated polysaccharides (fucoidan-like substances) extracted from the seaweed Saccharina japonica, RPI-27 and RPI-28, have high antiviral activity against SARS-CoV2 *in vitro,* much greater than does remdesivir, a nucleoside analogue prodrug used for treating severely ill COVID-19 patients [2]. Kwon et al. infected Vero-CCL81 cells, which express SARS-CoV2 receptor ACE2 (and also TMPRSS2), with SARS-CoV-2 at a multiplicity of infection (MOI) of 2.5×10^{-3} with varying dosages of polysaccharide to assess antiviral activity. Their most potent compound tested, RPI-27, is a high molecular weight, branched sulphated polysaccharide related to fucoidans. The EC50 value (the concentration of a drug that induces its half-maximal effective response) of RPI-27 was found to be $8.3 \pm 4.6\,\mu$g/m, i.e., $\sim$83 nM, whereas that of remdesivir is 11.4 μM. SARS-CoV2, which uses ACE2 as an entry receptor, also utilizes cell surface heparan sulphate proteoglycans (HSPG) as attachment receptors. The authors found that RPI-27 binds tightly to the spike-protein (S-protein) of SARS-CoV-2, suggesting that this interaction would interfere with S-protein binding to the HSPG co-receptor in host tissues, thereby inhibiting viral infection. Whether the RPI-27 action involves also its attachment to HSPG, so that attachment of the S-protein of SARS-CoV-2 to the HSPG is directly blocked, is not suggested, but seems likely as the antiviral activity of fucoidans is thought to be a combination of their attachment to cell surface HSPG, and hence blockage of viral attachment to HSPG, and of a virucidal effect caused by their binding to the virus itself [3]. None of the tested polysaccharides showed toxicity even at the highest concentration used. In fact, fucoidan is used widely in the far East as a food supplement; in contrast, remdesivir

*Correspondence to: Ruth F. Itzhaki, Institute of Population Aging, University of Oxford, 66 Banbury Road, Oxford OX2 6PR, UK. E-mail: ruth.itzhaki@manchester.ac.uk.

must be delivered intravenously. If RPI-27 were to be used for treating COVID-19 patients and proved successful, it would be of enormous benefit. The benefit might not just be immediate, as it might prevent future neurological manifestations in survivors and prevent also speculatively predicted outcomes such as certain neurodegenerative diseases, including Alzheimer's disease (AD) [4]. Such speculations would be warranted if SARS-CoV2 RNA or proteins were detectable in brain of COVID-19 patients and were found to remain there long-term in latent form, and if so, if the virus were shown to be reactivatable. Such information would be equally important also from COVID-19 subjects who are infected but are asymptomatic—estimated to be up to 45% of those infected (paralleling herpes simplex virus type 1 (HSV1) infection, in which at least half of those infected are asymptomatic: a major feature often not recognized previously, before its appearance in COVID-19).

It was recently suggested that the apparent success of another compound related to fucoidans, GV971, an unsulphated polysaccharide, which was used in a trial for treating AD patients [5], might be the result of its having antiviral activity, and that if sulphated to make its structure similar to a fucoidan, its postulated antiviral activity would greatly enhanced [6]. This explanation would be indirectly supported if the current antiviral trial for AD were to be successful [7]; unfortunately, though, the advent of COVID-19 has halted its progress.

Certainly, fucoidans derived from other types of seaweed, especially *Undaria pinnatifida*, show strong antiviral action against HSV1 *in vitro,* (and against several other types of virus *in vitro* and in humans [8]), greater than that of acyclovir (ACV, a nucleoside analogue used extensively to combat HSV1 infection), and it was found that the antiviral effect of fucoidan in combination with ACV is synergistic [9]. Thus, fucoidans have powerful protective effects at least *in vitro* against two very different types of virus, one of which is strongly implicated in AD.

Today the number of deaths from COVID-19 worldwide is about 1 million. The number of people who suffer from AD is about 30 million worldwide, and there is strong evidence suggesting that at least half are caused by HSV1 in brain (in *APOE* ε4 carriers). This number is hugely greater than that of COVID-19 patients' deaths, and in AD, death follows what is often a long drawn-out almost death-like existence. As mentioned, only one full antiviral trial for AD, of VCV (the prodrug of ACV), has been set up. Surely further types of antiviral trial, such as VCV plus a fucoidan, which would have the great advantage of using two quite different antiviral mechanisms, namely, inhibition of viral DNA synthesis and blockage of viral entry into cells, are urgently needed for treating AD as are further pre-clinical studies.

DISCLOSURE STATEMENT

The author's disclosure is available online (https://www.j-alz.com/manuscript-disclosures/20-0986r1).

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