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Ebselen, a new candidate therapeutic against SARS-CoV-2

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We read with great interest the recently published article by Abbasi-Oshaghi et al. that discussed the potential of repurposing FDA-approved drugs and other therapeutic strategies for managing COVID-19-associated deaths [1]. We would like to compliment, and add our analysis on another strategy that targets glutathione peroxidase 1 (GPX1) detoxifying system and the main protease (Mpro) of SARS-CoV-2 for treating COVID-19 patients. This is made possible by utilizing the GPX1-mimetic drug, ebselen.

The emergence of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) in China was accompanied by the need for developing specific therapeutics that can put an end to the ongoing pandemic. However, the development of a novel SARS-CoV-2-specific drug will take several years and cost billions because of the need to establish efficacy and long-term safety profiles. Therefore, the repurposing of already known drugs with well-established safety profiles can accelerate the evaluation process and shorten the gap between efficacy studies and their clinical utility. Recently, Jin et al. have assayed more than 10,000 compounds using a combination of structure-based virtual and high-throughput screening to identify efficient inhibitors of main protease (M^{pro}), a key enzyme of SARS-CoV-2. One of the six compounds that inhibited SARS-CoV-2 M^{pro}, ebselen (SPI-1005), also exhibited promising antiviral activity in cell-based assays [2]. Ebselen (2-phenyl-1, 2-benzoisoselenazol-3(2H)-one) is an organoselenium compound with hydroperoxide- and peroxynitrite-reducing activity (Figure - 1). Biologically it acts as an enzyme mimetic, catalyzing the glutathione peroxidase reaction [3]. Ebselen has also been reported to possess antioxidant, anti-inflammatory, and cytoprotective properties [2].

Ebselen has been previously found to exhibit potent antiviral activity against many viruses including human immunodeficiency virus type 1 (HIV-1) [4], hepatitis C virus (HCV) [5], influenza A virus [6], and Zika virus [7]. The antiviral activity of ebselen against HIV-1 is mediated via the inhibition of HIV-1 capsid protein, which has a central role in the events leading to viral infection [8]. Furthermore, the *in vitro* studies have validated that the antiviral activity of ebselen can also be attributed to its ability to interferes with the binding of chromatin-associated host cell molecule and lens-epithelium-derived growth-factor (LEDGF/p75) to HIV-1 integrase resulting in failure of viral genome integration to the host cell DNA [4]. However, the antiviral action of ebselen against the hepatitis C virus (HCV) is mediated via the inhibition of NS3 helicase activity that is required for viral assembly and replication but does not inhibit the protease activity [5].

Apart from promising antiviral activity, ebselen also possess anti-oxidant, anti-inflammatory, antimalarial, anti-trypanosomal and cyto-protective properties indicating a broad spectrum of activity [2,9,10]. Interestingly, ebselen is also considered for the prevention of noise-induced hearing loss and bipolar disorder, currently being studied in a phase-2 trial [11,12]. Early research on ebselen documented that it has numerous targets in biological pathways with a distinct mechanism of action and can be utilized for treating different clinical conditions, attributing to its broad spectrum of activity [13].

As an antiviral drug against SARS-CoV-2, ebselen acts through the inhibition of the main viral protease, M^{pro} [14]. The main protease is one of the crucial enzymes in the viral life cycle that plays a key role in viral replication and transcription process [15]. Inhibition of M^{pro} and subsequently, the nonstructural proteins (Nsps) arrests the process of viral assembly in the SARS-CoV-2 replication cycle, making it a promising drug for treating COVID-19 patients (Figure - 2). Studies using experimental animal models have demonstrated that ebselen, when given orally, effectively combats lung inflammation, possibly by inhibition of leukocyte infiltration, IL1β, TNFα, and inflammatory cytokines in the lungs [16]. Pre-treatment of mice with ebselen at the dose of 10 mg/kg given orally before intranasal inoculation and infection with influenza A virus (H3N2) have resulted in the significant reduction of virus titers, leukocyte count in bronchioalveolar lavage fluid, and expression of inflammatory cytokines [17]. Therefore, the anti-inflammatory activity exhibited by ebselen in the lungs can be utilized to treat COVID-19, as the primary target organ of SARS-CoV-2 is lungs. Further studies are required to evaluate the beneficial interaction of ebselen with the

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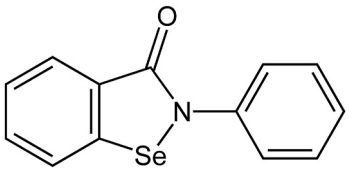

Fig. 1. Chemical structure of ebselen, an organoselenium compound that mimics glutathione peroxidase activity.

replication cycle of SARS-CoV-2.

Besides its direct antiviral activity against SARS-CoV-2, ebselen also possess excellent anti-inflammatory property owing to the thiol-mediated and peroxiredoxin-like inhibitory effects on inflammation. Ebselen is likely to exhibit potential effects in inflammatory conditions sequential to acute respiratory distress syndrome (ARDS), one of the primary reasons for mortality in COVID-19 patients [3]. Moreover, it is also reported that ebselen can correct the disturbances in iron homeostasis induced by stressful stimuli in rats [18]. The increased release of iron from the circulating ferritin in COVID-19 patients disturbs the iron homeostasis, thereby increasing the susceptibility to cytotoxicity and increased chances of mortality. Therefore, treatment with ebselen can further decrease the mortality rate in SARS-CoV-2 infection [19].

In the SARS-CoV-2 context, the proposed antiviral activity of ebselen identified based on crystallographic studies is mediated via the direct inhibition of the main protease through non-covalent binding with cysteine present in the active site of M^{pro} forming selenosulfide [2]. It has been also demonstrated that the ebselen at half-maximal effective concentration (EC50) value of 4.67 μM has exhibited inhibitory activity against SARS-CoV-2 in cell-based assays. Furthermore, the dose-response curve suggests it can penetrate the cell membranes and access their targets [2]. Even though the antiviral activity of ebselen is well documented based on in silico and *in vitro* studies, further investigation is warranted using *in vivo* studies with suitable animal models. Additional studies are also required to investigate whether ebselen affects capsid formation and viral replication in SARS-CoV-2, as in the case of HIV-1 or HCV [3].

It has also been proven that ebselen is capable of inhibiting liver injury induced by chemical and microbial stimuli [20]. One of the most common findings observed in severe cases of COVID-19 is liver injury [21]. Therefore, treatment with ebselen might also have added benefits in this particular aspect of the disease. Moreover, ebselen is also found to be effective in managing focal ischemic injury by decreasing IL-6 [22], which can protect SARS-CoV-2 infected patients with venous thrombosis and vascular injury [23]. Nevertheless, the findings of these previous studies give us hope for the therapeutic potential of ebselen in managing COVID-19. Further investigations are required using randomized clinical control trials before they can be included in any treatment regimen. Considering the therapeutic potential of ebselen in COVID-19, two major clinical trials have already been registered to evaluate the safety and efficacy of this repurposed drug in moderate and severe COVID-19 patients (Table 1).

Although ebselen exhibits potential antiviral activity against SARS-CoV-2, its effectiveness can be impeded by certain unknown factors and therefore require further studies. For successful therapeutic use, ebselen must attain therapeutic plasma concentration sufficient to exert antiviral action. The inhibition of M^{pro} can be efficiently increased via the combination of ebselen with *N*-acetyl cysteine, a drug with cytoprotective effects that can act against SARS-CoV-2 by inhibiting virus replication, attributing to its synergistic action against the virus [24,25]. Since ebselen already possess antiviral activity against several viruses and exhibits potent antiviral activity against SARS-CoV-2 via M^{pro} inhibition [2], assuming the same is realized in the *in vivo* and clinical studies, repurposing it for SARS-CoV-2 treatment seems to be a reasonable option [3]. Therefore, ebselen can be considered as a potential therapeutic candidate for COVID-19 patients. However, before including it in the treatment guidelines and widespread use as a potential antiviral drug, further studies should be undertaken to establish its efficacy using *in vitro*, *in vivo*, and clinical studies.

Ethical approval

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Author contribution

All authors equally contributed to the analysis and writing of the manuscript.

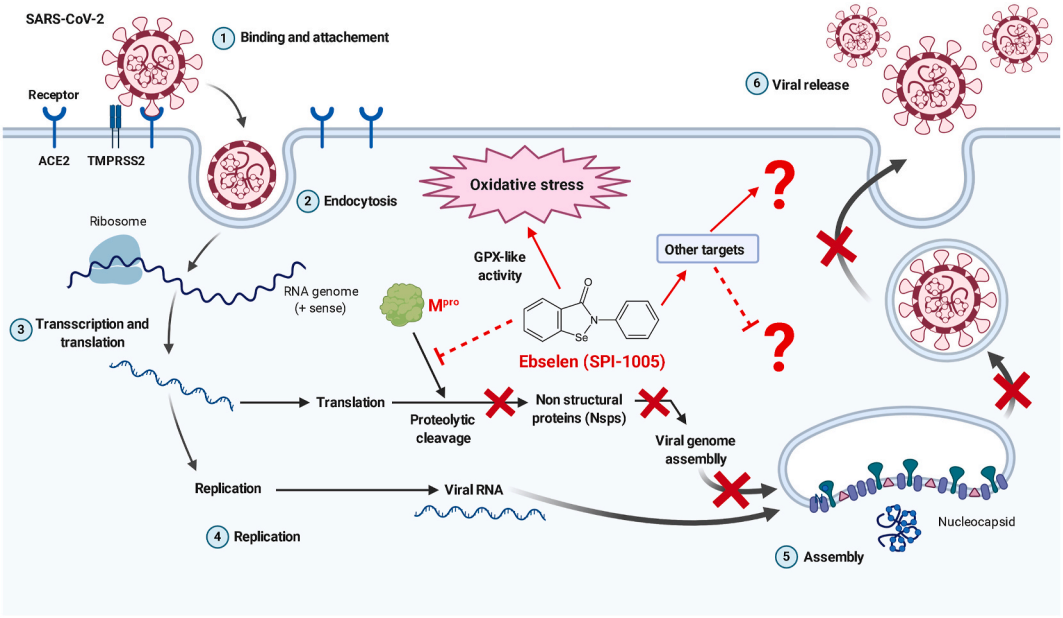

Fig. 2. Ebselen exhibits antiviral activity against SARS-CoV-2 via the inhibition of the main viral protease (M^{pro}).

Table 1
Clinical trials evaluating the therapeutic efficacy and safety of ebselen (SPI-1005) in COVID-19 patients (www.clinicaltrials.gov).

NCT No.	Title	Status	Phase	Population	Interventions
NCT04484025	SPI-1005 Treatment in Moderate COVID-19 Patients	Not yet recruiting	Phase 2	60 participants (18 years and older)	Arm 1–400 mg BID orally for 7 days Arm 2–800 mg BID orally for 7 days
NCT04483973	SPI-1005 Treatment in Severe COVID-19 Patients	Not yet recruiting	Phase 2	60 participants (18 years and older)	Arm 1–400 mg BID orally for 7 days Arm 2–800 mg BID orally for 7 days

Trial registry number

1. Name of the registry: Not applicable.
2. Unique Identifying number or registration ID: Not applicable.
3. Hyperlink to your specific registration (must be publicly accessible and will be checked): Not applicable.

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Data statement

Data sharing is not applicable to this article as no new data were created or analysed in this study.

Declaration of competing interest

All authors declare that there exist no commercial or financial relationships that could, in any way, lead to a potential conflict of interest.

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