Marine mollusc extracts—Potential source of SARS-CoV-2 antivirals

Rebecca L. Pedler | Peter G. Speck

College of Science and Engineering, Flinders University, Bedford Park, South Australia, Australia

Correspondence
Peter G. Speck, College of Science and Engineering, Flinders University, Bedford Park, GPO Box 2100, Adelaide 5001, South Australia, Australia.
Email: peter.speck@flinders.edu.au

Summary
Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel human coronavirus and the causative agent of coronavirus disease 2019 (Covid-19). There is an urgent need for effective antivirals to treat current Covid-19 cases and protect those unable to be vaccinated against SARS-CoV-2. Marine molluscs live in an environment containing high virus densities (>10^7 virus particles per ml), and there are an estimated 100,000 species in the phylum Mollusca, demonstrating the success of their innate immune system. Mollusc-derived antivirals are yet to be used clinically despite the activity of many extracts, including against human viruses, being demonstrated in vitro. Hemolymph of the Pacific oyster (Crassostrea gigas) has in vitro antiviral activity against herpes simplex virus and human adenovirus, while antiviral action against SARS-CoV-2 has been proposed by in silico studies. Such evidence suggests that molluscs, and in particular C. gigas hemolymph, may represent a source of antivirals for human coronaviruses.

KEYWORDS
human coronaviruses, molluscs, Pacific oyster (Crassostrea gigas), SARS-CoV-2 antivirals

1 | INTRODUCTION

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a novel human coronavirus which emerged in Wuhan, China during December 2019.1–3 SARS-CoV-2 is the causative agent of the coronavirus disease 2019 (Covid-19) and as of August 2021, has infected more than 196 million people globally and resulted in over 4.2 million deaths.4 Although vaccination will likely form the path out of the SARS-CoV-2 pandemic, effective antivirals are still required to treat current Covid-19 cases and protect those unable or unwilling to be vaccinated.2,5,6 or in whom vaccines have poor efficacy. The efficacy of vaccines and antivirals currently in clinical trials are also threatened by the ongoing emergence of new SARS-CoV-2 variants.7–9 Since March 2020, several SARS-CoV-2 variants of concern (VOC), including the alpha, beta, gamma and more recently, delta strain have emerged with discernible changes in epidemiology and transmissibility.10,11 Immune-modulating agents to control the excessive inflammation seen in Covid-19 will play an important role,12 and this will be complemented by development of better antiviral drugs. As the science community continues to tackle a moving target, ongoing research to identify novel antiviral compounds against SARS-CoV-2 is crucial.

2 | CURRENT STATUS OF SARS-CoV-2 ANTIVIRAL DRUG DISCOVERY

Human coronaviruses are enveloped, single stranded RNA viruses that can further be classified as alpha-coronaviruses (human coronavirus-229E (HCoV-229E) and HCoV-NL63) or beta-coronaviruses (HCoV-OC43, HCoV-HKU1, Middle Eastern...
there are over 100,000 species of mollusc, some of which live over 400 years, such as the ocean quahog, Arctica islandica. Molluscan antiviral compounds can be sourced exogenously from their algae-based diets, continuously expressed, or transiently expressed in response to viral challenge.\textsuperscript{26,38,39} Molluscs derived antivirals are yet to be used clinically despite the activity of many extracts, against human viruses, being demonstrated \textit{in vitro}.\textsuperscript{40,41} As listed in Table 1, numerous marine mollusc extracts have been shown to have antiviral activity. The circulatory fluid (hemolymph) and lipophilic digestive gland extract of greenlip abalone (Haliotis laevigata), has been shown to inhibit herpes simplex virus 1 (HSV-1) in Vero cells.\textsuperscript{30} Time-of-addition assays suggested that \textit{H. laevigata} hemolymph either inhibited the entry of HSV-1 into Vero cells or was internalised simultaneously with the virus and acted during an early intracellular stage of infection.\textsuperscript{30} \textit{Haliotis laevigata} lipophilic digestive gland likely inhibits an intracellular stage of HSV-1 infection.\textsuperscript{30} Inhibition of HSV-1 has also been observed \textit{in vitro} using extracts from the common cockle (Cerastoderma edule), Japanese carpet shell (Ruditapes philippinarum), European flat oyster (Ostrea edulis), common whelk (Buccinum undatum),\textsuperscript{41} blacklip abalone (\textit{Haliotis rubra}),\textsuperscript{42,43} veined rapa whelk (\textit{Rapana venosa})\textsuperscript{44} and the Mediterranean mussel (\textit{Mytilus galloprovincialis}).\textsuperscript{45} Early work involving oral administration of aqueous extracts from canned red abalone (\textit{Haliotis rufescens}), in Swiss mice, showed protection against poliovirus and influenza A.\textsuperscript{46,47} Antiviral activity against poliovirus has also been observed using paolin II, an extract from the Eastern oyster (\textit{Crassostrea virginica}).\textsuperscript{48}

### 3 | MARINE MOLLUSCS AS A SOURCE OF ANTIVIRAL COMPOUNDS

Marine invertebrates represent an almost totally unexploited source of medicinal compounds.\textsuperscript{6,26–28} Marine invertebrates lack an adaptive immune system and only have the capacity to elicit innate immune responses,\textsuperscript{29–31} despite living in an environment which contains virus particles in the order of \textgreater 10\textsuperscript{7} per ml.\textsuperscript{12,23} This demonstrates the success of their innate immunity, which includes the production of potent antiviral compounds.\textsuperscript{28,30} The nucleosides spongouridine and spongouridine, which contain D-arabinose rather than D-ribose, were isolated in the 1950s from the marine sponge, Tectitethya crypta (formerly \textit{Cryptotheca crypta}), and this led to the development of the only marine invertebrate derived antiviral drug currently available on the market, vidarabine.\textsuperscript{6,28,30} Vidarabine later inspired the design of antiviral drugs, acyclovir, and zidovudine.\textsuperscript{28,34} Acyclovir and vidarabine are both nucleoside analogues which inhibit the nucleic acid synthesis of certain herpesviruses\textsuperscript{6,35} while zidovudine is a nucleoside reverse transcriptase inhibitor (NRTI) used in treatment of human immunodeficiency virus (HIV).\textsuperscript{36} The success of vidarabine, zidovudine and acyclovir exemplify how marine invertebrates not only represent a direct source of antiviral compounds but can also inspire the synthesis of novel antivirals.

Marine organisms of the phylum Mollusca are responsible for much of the diversity among marine invertebrates, and it is estimated that)..
chaperone.\textsuperscript{52} it is possible that \textit{C. gigas} cavortin has potential antiviral activity against SARS-CoV-2 and may also act as a metal chaperone which facilitates movement of zinc into host cells.

The discovery of antiviral agents is challenged by the limited number of laboratories which have the appropriate biosafety containment level for working with SARS-CoV-2.\textsuperscript{5,61} HCoV-229E is a related coronavirus responsible for mild infections resembling the common cold.\textsuperscript{62,63} HCoV-229E can be handled in lesser-rated laboratories making it more accessible for research on human coronaviruses\textsuperscript{64} and this virus could be used for initial screening for anti-coronavirus activity. Identification of potential new antiviral compounds against human coronaviruses will have considerable relevance in the current COVID-19 pandemic.

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\section*{CONFLICT OF INTEREST}
The authors declare no conflict of interests.

\section*{AUTHOR CONTRIBUTIONS}
Peter G. Speck was involved in conception, writing and editing. Rebecca L. Pedler was involved in writing and editing.

\section*{DATA AVAILABILITY STATEMENT}
Not applicable.

\section*{ORCID}
Peter G. Speck \url{https://orcid.org/0000-0001-9087-258X}

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