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REVIEW

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

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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

Abbreviations: ACE2, angiotensin converting enzyme 2; Adv-5, Adenovirus type 5; Covid-19, coronavirus disease 2019; EBV, Epstein-Barr virus; HCoV, human coronavirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; MERS, Middle Eastern respiratory syndrome; NRTI, nucleoside reverse transcriptase inhibitor; RNA, ribonucleic acid; RdRp, RNA dependant RNA polymerase; SARS-CoV-2, severe acute respiratory syndrome 2; SOD, superoxide dismutase; SPE, solid phase extraction; VOC, variants of concern.

respiratory syndrome (MERS-CoV), SARS-CoV and SARS-CoV-2).[13] Human coronaviruses contain characteristic spike glycoproteins embedded within the viral envelope.[14] The SARS-CoV-2 spike glycoprotein facilitates entry into host cells by binding to the angiotensin converting enzyme 2 (ACE-2) receptor on the host cell surface.[15] Host proteases, TMPRSS2 and furin have also been established as important enzymes for priming SARS-CoV-2 spike glycoproteins upon binding to ACE2.[15] Blocking of this binding process, along with other stages of the SARS-CoV-2 infectious cycle (viral uncoating, genome replication and virion release) remain targets for development of new antiviral drugs.[16]

An alternative route for SARS-CoV-2 antiviral discovery has been the repurposing of currently approved drugs.[16–18] Remdesivir is a nucleotide prodrug of an adenosine analogue which inhibits the RNA-dependent RNA polymerase (RdRp) of filoviruses.[17] Promising randomised trials[19,20] and *in vitro* studies[21] have led to the approval of remdesivir to treat SARS-CoV-2 infection in Europe and the United States.[17] Despite gaining approval, data from subsequent clinical trials shows remdesivir has failed to emerge as highly efficacious Covid-19 treatment.[22,23] The antimalaria drug hydroxychloroquine showed promising *in vitro* activity against SARS-CoV-2[21] however, it has yielded poor results in randomised clinical trials.[24] Several other repurposing targets have been flagged, including favipiravir, lopinavir-ritonavir, ribavirin, ivermectin and oseltamivir.[16,18,25] Despite repurposing efforts, robust antiviral treatments for SARS-CoV-2 are yet to be identified.

3 | MARINE MOLLUSCS AS A SOURCE OF ANTIVIRAL COMPOUNDS

Marine invertebrates represent an almost totally unexploited source of medicinal compounds.[6,26–28] Marine invertebrates lack an adaptive immune system and only have the capacity to elicit innate immune responses,[29–31] despite living in an environment which contains virus particles in the order of $>10^7$ per ml.[32,33] This demonstrates the success of their innate immunity, which includes the production of potent antiviral compounds.[28,30] The nucleosides spongothymidine and spongouridine, which contain D-arabinose rather than D-ribose, were isolated in the 1950s from the marine sponge, *Tectitethya crypta* (formerly *Cryptoethia crypta*), and this led to the development of the only marine invertebrate derived antiviral drug currently available on the market, vidarabine.[6,28,30] Vidarabine later inspired the design of antiviral drugs, acyclovir, and zidovudine.[28,34] Acyclovir and vidarabine are both nucleoside analogues which inhibit the nucleic acid synthesis of certain herpesviruses[6,35] while zidovudine is a nucleoside reverse transcriptase inhibitor (NRTI) used in treatment of human immunodeficiency virus (HIV).[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 there are over 100,000 species of mollusc,[26] some of which live over 400 years, such as the ocean quahog, *Arctica islandica*.[37] Molluscan antiviral compounds can be sourced exogenously from their algae-based diets,[26] continuously expressed, or transiently expressed in response to viral challenge.[26,38,39] Mollusc derived antivirals are yet to be used clinically despite the activity of many extracts, against human viruses, being demonstrated *in vitro*.[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.[40] Time-of-addition assays suggested that *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.[40] *Haliotis laevigata* lipophilic digestive gland likely inhibits an intracellular stage of HSV-1 infection.[40] Inhibition of HSV-1 has also been observed *in vitro* using extracts from the common cockle (*Cerastoderma edule*), Japanese carpet shell (*Ruditapes philippinarum*), European flat oyster (*Ostrea edulis*), common whelk (*Buccinum undatum*),[41] blacklip abalone (*Haliotis rubra*),[42,43] veined rapa whelk (*Rapanosa venosa*)[44] and the Mediterranean mussel (*Mytilus galloprovincialis*).[45] Early work involving oral administration of aqueous extracts from canned red abalone (*Haliotis rufescens*), in Swiss mice, showed protection against poliovirus and influenza A.[46,47] Antiviral activity against poliovirus has also been observed using paolin II, an extract from the Eastern oyster (*Crassostrea virginica*).[48]

4 | PACIFIC OYSTER (*Crassostrea gigas*) HEMOLYMPH—POTENTIAL SARS-CoV-2 ANTIVIRAL?

The Pacific oyster (*Crassostrea gigas*) is an economically important marine mollusc cultured globally.[49] The hemolymph of *C. gigas* has antiviral activity *in vitro*.[49–51] The major *C. gigas* hemolymph protein, cavortin, also exerts an antiviral effect against HSV-1 in Vero cells.[49] The specific mechanism behind cavortin's antiviral activity, along with its bioavailability in cell culture and/or animal models, remains unknown and presents questions for future research. Despite this, a direct virucidal effect of cavortin against HSV-1 has been identified.[49] Time of addition assays have also suggested that cavortin acts on an intracellular stage of HSV-1 infection.[49] Cavortin is a protein of approximately Mr 20,000, containing a single copper/zinc superoxide dismutase (SOD) domain.[52,53] There is evidence to suggest that the SOD activity of cavortin has been lost in evolution and its primary role is as a metal chaperone.[52] Intracellular zinc can inhibit SARS-CoV enzymes: RNA dependent RNA polymerase,[54] 3C-like protease[55] and papain-like protease 2[56] which are important in viral replication. Zinc may also have potential to act as a therapeutic for SARS-CoV-2.[57–59] The efficacy of zinc as an antiviral for human coronaviruses is improved by coupling with a metal chaperone.[54,58] *C. gigas* has a high zinc content[60] and given the suggested role for cavortin as a metal

TABLE 1 Proposed mode of action for marine mollusc antiviral extracts

Mollusc	Antiviral extract	Mode of action	Virus(s)	Reference(s)
Greenlip abalone (*Haliotis laevigata*)	Hemolymph	Inhibits viral entry	HSV-1	40,43
	Lipophillic digestive extract	Inhibits intracellular stage of viral infection	HSV-1	40
Blacklip abalone (*Haliotis rubra*)	Hemocyanin	Inhibits viral entry	HSV-1	42,65
	Hemolymph	Unknown	HSV-1	43
Red abalone (*Haliotis rufescens*)	Aqueous extract	Unknown	Poliovirus, Influenza A	46,47
Pacific oyster (*Crassostrea gigas*)	Major hemolymph protein (cavortin)	Inhibits intracellular stage of viral infection	HSV-1	49
		Inhibits viral entry	HSV-1	50
	Hemolymph	Unknown	HSV-1, AdV-5	51
Eastern oyster (*Crassostrea virginica*)	Paolin II	Unknown	Poliovirus	48
Mangrove oyster (*Crassostrea rhizophorae*)	Hemolymph	Inhibits intracellular stage of viral infection	AdV-5, HSV-1	51
European flat oyster (*Ostrea edulis*)	40% SPE-fraction from gill and mantle	Unknown	HSV-1	41
Mediterranean mussel (*Mytilus galloprovincialis*)	Myticin C peptide	Inhibits intracellular stage of viral infection	HSV-1, HSV-2	45
Japanese carpet shell (*Ruditapes philippinarum*)	40% SPE-fraction	Unknown	HSV-1	41
Common whelk (*Buccinum undatum*)	40% SPE-fraction	Unknown	HSV-1	41
Veined rapa whelk (*Rapanosa venosa*)	Hemocyanin	Unknown	EBV	44,66
Common cockle (*Cerastoderma edule*)	Acidic extract	Unknown	HSV-1	41

Abbreviations: AdV-5, human adenovirus type 5; EBV, Epstein–Barr virus; HSV, herpes simplex virus; SPE, solid phase extraction.

chaperone,[52] it is possible that *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.[5,61] HCoV-229E is a related coronavirus responsible for mild infections resembling the common cold.[62,63] HCoV-229E can be handled in lesser-rated laboratories making it more accessible for research on human coronaviruses[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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None.

CONFLICT OF INTEREST

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

Peter G. Speck was involved in conception, writing and editing. Rebecca L. Pedler was involved in writing and editing.

DATA AVAILABILITY STATEMENT

Not applicable.

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REFERENCES

1. Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. *Lancet*. 2020;395:470-473.
2. Ghanbari R, Teimoori A, Sadeghi A, et al. Existing antiviral options against SARS-CoV-2 replication in COVID-19 patients. *Future Microbiol*. 2021;15.
3. Triggle CR, Bansal D, Ding H, et al. A comprehensive review of viral characteristics, transmission, pathophysiology, immune response, and management of SARS-CoV-2 and COVID-19 as a basis for controlling the pandemic. *Front Immunol*. 2021;12:631139.
4. World Health Organisation. *WHO Coronavirus disease (COVID-19) dashboard*; 2021. [Online].
5. Hall MD, Anderson JM, Anderson A, et al. Report of the National Institutes of Health SARS-CoV-2 Antiviral Therapeutics Summit. *J Infect Dis*. 2021;224:S1-S21.
6. Riccio G, Ruocco N, Mutalipassi M, et al. Ten-year research update review: antiviral activities from marine organisms. *Biomolecules*. 2020;10:1-36.
7. Planas D, Veyer D, Baidaliuk A, et al. Reduced sensitivity of SARS-CoV-2 variant delta to antibody neutralization. *Nature*. 2021;596:276-280.

8. Olliaro P, Torreele E, Vaillant M. COVID-19 vaccine efficacy and effectiveness—the elephant (not) in the room. *Lancet Microbe*. 2021;2:e279-e280.
9. Baum A, Fulton BO, Wloga E, et al. Antibody cocktail to SARS-CoV-2 spike protein prevents rapid mutational escape seen with individual antibodies. *Science*. 2020;369:1014-1018.
10. World Health Organisation. *Tracking SARS-CoV-2 Variants*; 2021. [Online].
11. Ong DSY, Koeleman JGM, Vaessen N, Breijer S, Paltansing S, de Man P. Rapid screening method for the detection of SARS-CoV-2 variants of concern. *J Clin Virol*. 2021;141:104903.
12. Buonaguro FM, Ascierto PA, Morse GD, et al. Covid-19: time for a paradigm change. *Rev Med Virol*. 2020;30:e2134.
13. Woo PCY, Huang Y, Lau SKP, Yuen K-Y. Coronavirus genomics and bioinformatics analysis. *Viruses*. 2010;2:1805-1820.
14. Cueno ME, Imai K. Structural comparison of the SARS-CoV-2 spike protein relative to other human-infecting coronaviruses. *Front Med*. 2021;7:594439.
15. Hoffmann M, Kleine-Weber H, Schroeder S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. *Cell*. 2020;181:271-280.e278.
16. Indari O, Jakhmola S, Manivannan E, Jha HC. An update on antiviral therapy against SARS-CoV-2: how far have we come? *Front Pharmacol*. 2021;12:632677.
17. Martinez MA. Lack of effectiveness of repurposed drugs for COVID-19 treatment. *Front Immunol*. 2021;12:635371.
18. Martinez MA. Compounds with therapeutic potential against novel respiratory 2019 coronavirus. *Antimicrob Agents Chemother*. 2020;64.
19. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the treatment of Covid-19—final report. *N Engl J Med*. 2020;383:1813-1826.
20. Spinner CD, Gottlieb RL, Criner GJ, et al. Effect of remdesivir vs standard care on clinical status at 11 days in patients with moderate Covid-19: a randomized clinical trial. *J Am Med Assoc*. 2020;324:1048-1057.
21. Wang M, Cao R, Zhang L, et al. Remdesivir and chloroquine effectively inhibit the recently emerged novel coronavirus (2019-nCoV) in vitro. *Cell Res*. 2020;30:269-271.
22. Goldman JD, Lye DCB, Hui DS, et al. Remdesivir for 5 or 10 days in patients with severe Covid-19. *N Engl J Med*. 2020;383:1827-1837.
23. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *Lancet*. 2020;395:1569-1578.
24. Abella BS, Jolkovsky EL, Biney BT, et al. Efficacy and safety of hydroxychloroquine vs placebo for pre-exposure SARS-CoV-2 prophylaxis among health care workers: a randomized clinical trial. *JAMA Intern Med*. 2021;181:195-202.
25. Tan Q, Duan L, Ma Y, et al. Is oseltamivir suitable for fighting against COVID-19: *in silico* assessment, in vitro and retrospective study. *Bioorg Chem*. 2020;104:104257.
26. Benkendorff K. Molluscan biological and chemical diversity: secondary metabolites and medicinal resources produced by marine molluscs. *Biol Rev Camb Philos Soc*. 2010;85:757-775.
27. Summer K, Browne J, Liu L, Benkendorff K. Molluscan compounds provide drug leads for the treatment and prevention of respiratory disease. *Mar Drugs*. 2020;18:570.
28. Sagar S, Kaur M, Minneman KP. Antiviral lead compounds from marine sponges. *Mar Drugs*. 2010;8:2619-2638.
29. Agius JR, Corbeil S, Helbig KJ. Immune control of herpesvirus infection in molluscs. *Pathogens*. 2020;9:1-11.
30. Dang VT, Benkendorff K, Green T, Speck P. Marine snails and slugs: A great place to look for antiviral drugs. *J Virol*. 2015;89:8114-8118.
31. Tiscar PG, Mosca F. Defense mechanisms in farmed marine molluscs. *Vet Res Commun*. 2004;28:57-62.
32. Bratbak G, Heldal M, BØrsheim KY, Ø Bergh. High abundance of viruses found in aquatic environments. *Nature*. 1989;340:467-468.
33. Suttle CA. Marine viruses – major players in the global ecosystem. *Nat Rev Microbiol*. 2007;5:801-812.
34. Clercq ED. New anti-HIV agents and targets. *Med Res Rev*. 2002;22:531-565.
35. Darby G. The acyclovir legacy: its contribution to antiviral drug discovery. *J Med Virol*. 1993;41:134-138.
36. Darbyshire JH. Delta: a randomised double-blind controlled trial comparing combinations of zidovudine plus didanosine or zalcitabine with zidovudine alone in HIV-infected individuals. *Lancet*. 1996;348:283-291.
37. Abele D, Strahl J, Brey T, Philipp EER. Imperceptible senescence: ageing in the ocean quahog Arctica islandica. *Free Radic Res*. 2008;42:474-480.
38. Green TJ, Raftos D, Speck P, Montagnani C. Antiviral immunity in marine molluscs. *J Gen Virol*. 2015;96:2471-2482.
39. He Y, Jouaux A, Ford SE, et al. Transcriptome analysis reveals strong and complex antiviral response in a mollusc. *Fish Shellfish Immunol*. 2015;46:131-144.
40. Dang VT, Benkendorff K, Speck P. In vitro antiviral activity against herpes simplex virus in the abalone *Haliotis laevigata*. *J Gen Virol*. 2011;92:627-637.
41. Defer D, Bourgougnon N, Fleury Y. Screening for antibacterial and antiviral activities in three bivalve and two gastropod marine molluscs. *Aquaculture*. 2009;293:1-7.
42. Talaei Zanjani N, Miranda-Saksena M, Valtchev P, et al. Abalone hemocyanin blocks the entry of herpes simplex virus 1 into cells: a potential new antiviral strategy. *Antimicrob Agents Chemother*. 2016;60:1003-1012.
43. Dang VT, Speck P, Doroudi M, Smith B, Benkendorff K. Variation in the antiviral and antibacterial activity of abalone *Haliotis laevigata*, *H. rubra* and their hybrid in South Australia. *Aquaculture*. 2011;315:242-249.
44. Nesterova NV, Zagorodnya SD, Moshtanska V, et al. Antiviral activity of hemocyanin isolated from marine snail *Rapana venosa*. *Antivir Res*. 2011;90:A38.
45. Novoa B, Romero A, Álvarez ÁL, et al. Antiviral activity of myticin C peptide from mussel: an ancient defense against herpesviruses. *J Virol*. 2016;90:7692-7702.
46. Li C, Precott B, Jahnes W. Antiviral activity of a fraction of abalone juice. *Exp Biol Med*. 1962;109:534-538.
47. Li C. Antimicrobial effect of abalone juice. *Proc Soc Exo Biol Med*. 1960;103:522-524.
48. Prescott B, Li C, Caldes G, Martino E. Chemical studies of Paolin. II. An antiviral substance from oysters. *Proc Soc Exo Biol Med*. 1966;123:460-464.
49. Green TJ, Robinson N, Chataway T, Benkendorff K, O'Connor W, Speck P. Evidence that the major hemolymph protein of the Pacific oyster, *Crassostrea gigas*, has antiviral activity against herpesviruses. *Antivir Res*. 2014;110:168-174.
50. Olicard C, Renault T, Torhy C, Benmansour A, Bourgougnon N. Putative antiviral activity in hemolymph from adult Pacific oysters, *Crassostrea gigas*. *Antivir Res*. 2005;66:147-152.
51. Carriel-Gomes MC, Kratz JM, Muller VDM, Barardi CRM, Simues CMO. Evaluation of antiviral activity in hemolymph from oysters *Crassostrea rhizophorae* and *Crassostrea gigas*. *Aquat Living Resour*. 2006;19:189-193.
52. Scotti PD, Dearing SC, Greenwood DR. Characterisation of cavortin, the major haemolymph protein of the Pacific oyster (*Crassostrea gigas*). *N Z J Mar Freshw Res*. 2007;41:91-101.
53. Gonzalez M, Romestand B, Fievet J, et al. Evidence in oyster of a plasma extracellular superoxide dismutase which binds LPS. *Biochem Biophys Res Commun*. 2005;338:1089-1097.

54. te Velthuis AJW, van den Worml SHE, Sims AC, Baric RS, Snijder EJ, van Hemert MJ. Zn^{2+} inhibits coronavirus and arterivirus RNA polymerase activity in vitro and zinc ionophores block the replication of these viruses in cell culture. *PLoS Pathog*. 2010;6:e1001176.
55. Lee C-C, Kuo C-J, Hsu M-F, et al. Structural basis of mercury- and zinc-conjugated complexes as SARS-CoV 3C-like protease inhibitors. *FEBS Lett*. 2007;581:5454-5458.
56. Han Y-S, Chang G-G, Juo C-G, et al. Papain-like protease 2 (PLP2) from severe acute respiratory syndrome coronavirus (SARS-CoV): expression, purification, characterization and inhibition. *Biochemistry*. 2005;44:10349-10359.
57. Carlucci PM, Ahuja T, Petrilli C, Rajagopalan H, Jones S, Rahimian J. Zinc sulfate in combination with a zinc ionophore may improve outcomes in hospitalized COVID-19 patients. *J Med Microbiol*. 2020;69:1228-1234.
58. Brewer J, Gomez Marti JL, Brufsky A. Potential interventions for SARS-CoV-2 infections: zinc showing promise. *J Med Virol*. 2021;93:1201-1203.
59. Asl SH, Nikfarjam S, Majidi Zolbanin N, Nassiri R, Jafari R. Immunopharmacological perspective on zinc in SARS-CoV-2 infection. *Int Immunopharmacol*. 2021;96:107630.
60. Kong N, Zhao Q, Liu C, et al. The involvement of zinc transporters in the zinc accumulation in the Pacific oyster *Crassostrea gigas*. *Gene*. 2020;750:144759.
61. Kaufer AM, Theis T, Lau KA, Gray JL, Rawlinson WD. Laboratory biosafety measures involving SARS-CoV-2 and the classification as a risk group 3 biological agent. *Pathology*. 2020;52:790-795.
62. Gralinski LE, Baric RS. Molecular pathology of emerging coronavirus infections. *J Pathol*. 2015;235:185-195.
63. Mei M, Tan X. Current strategies of antiviral drug discovery for Covid-19. *Front Mol Biosci*. 2021;8:671263.
64. Bracci N, Pan H-C, Lehman C, Kehn-Hall K, Lin S-C. Improved plaque assay for human coronaviruses 229E and OC43. *PeerJ*. 2020;8:e10639.
65. Zanjani NT, Sairi F, Marshall G, et al. Formulation of abalone hemocyanin with high antiviral activity and stability. *Eur J Pharm Sci*. 2014;53:77-85.
66. Dolashka P, Nesterova N, Zagorodnya S, et al. Antiviral activity of hemocyanin *Rapana venosa* and its isoforms against Epstein-Barr virus. *Global J Pharmacol*. 2014;8:206-212.

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