Available online at www.sciencedirect.com

ScienceDirect

Biomedical Journal

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

Review Article

Exploring algae and cyanobacteria as a promising natural source of antiviral drug against SARS-CoV-2

*Neha Sami, Rakhshan Ahmad, Tasneem Fatma**

Cyanobacterial Biotechnology Lab, Department of Biosciences, Jamia Millia Islamia, New Delhi, India

Dr. Tasneem Fatma

ARTICLE INFO

Article history:
Received 24 August 2020
Accepted 30 November 2020
Available online 7 December 2020

Keywords:
Coronavirus
2019-nCoV
Algal compounds

ABSTRACT

The present outburst of coronavirus-associated (SARS-CoV-2) acute respiratory disease coronavirus disease 19 (COVID-19) in December 2019 in Wuhan, China is the third recognised spill over due to the zoonotic transmission. SARS-CoVs are about 29.7 kb positive, single stranded (ss) RNA viruses that are considered as zoonotic pathogens, bat being their natural reservoirs and also shows transmission within humans. The rapidly increasing COVID-19 cases and need of best and efficient drug/vaccine/strategy to counteract the virus entry and its pathogenesis has made it a Herculean challenge for scientists. Synthetic drugs associated complications has attracted scientific attention for natural product-based drugs. Chemo-diversity of algae and cyanobacteria offers a novel approach and can be recognized as a relevant source for developing a future natural "antiviral drug". The aim of this review is to highlight important features of SARS-CoV-2/COVID-19 and the antiviral compounds recognized in algae and cyanobacteria, with their mechanisms of actions. Algae possess both immunity improving capacity and suppresses many viruses. Thus, they can be recommended as a preventive and curative remedy against SARS-CoV-2.

Coronavirus (CoV) has caused two large-scale pandemics in the last two decades i.e. Severe Acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [1]. An increasing number of patients with pneumonia occurred in Hubei province of Wuhan, China since December 2019, which has globally attracted attention [2]. World Health Organization (WHO) has named the novel pneumonia as Corona Virus Disease 19 (COVID-19), where 'CO' stands for corona, 'VI' for virus, 'D' for disease and the epithet 19 symbolises the year of outbreak i.e. 2019 and declared it as the sixth "Public Health Emergency of International Concern" (PHEIC) on 30th January 2020 and a "Global Pandemic" on 11th March 2020 [3].

* *Corresponding author*. Department of Biosciences, Jamia Millia Islamia, Maulana Mohammad Ali Jauhar Marg, Jamia Nagar, New Delhi 110025, India.
E-mail address: fatma_cbl@yahoo.com (T. Fatma).

Peer review under responsibility of Chang Gung University.
https://doi.org/10.1016/j.bj.2020.11.014

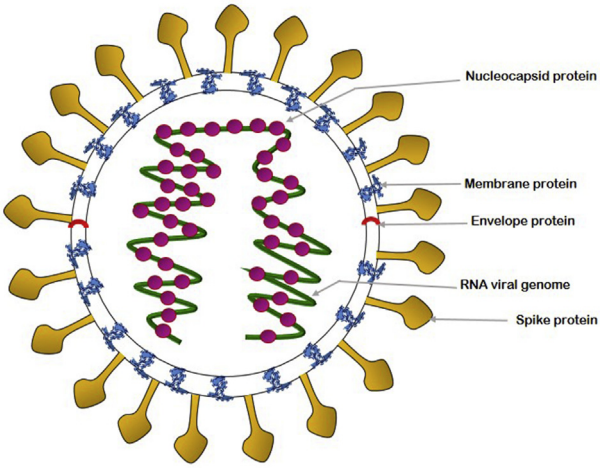

Fig. 1 Structure of SARS-CoV-2 virus.

Scientists have successfully isolated a novel coronavirus from human airway epithelial cells [Fig. 1] [4]. The high virulence of these viruses and the absence of effective therapies has posed an ongoing threat to the public health. The conventional one-bug-one-drug hypothesis is inadequate to discourse the challenge of emerging and re-emerging viral pathogens, and only few drugs are available at present to control the viral diseases [5]. Moreover, identification of targets is equally necessary to find highly specific drugs. Recently, Angiotensin-converting enzyme 2 (ACE2) expressing cells along with spike protein (S-protein) and non-structural proteins (nsp) have been identified as the target cells for neutralizing antibody and antiviral peptides that can prove to be the potential therapeutic target against SARS-CoV-2 [6]. Thus, the development of a broad-spectrum class of natural antiviral agents that bind to these specific targets is urgent in view of the global pandemic.

Algae and cyanobacteria are one of the richest sources of bioactive compounds that exhibit antiviral properties and are pharmacologically active [7]. Metabolites like flavanones, flavonols, and alkaloids are known to inhibit proteins like 3CLpro, Transmembrane Serine Protease 2 (TMPRSS2) and ACE2 involved in replication of COVID-19. Consequently, the antiviral compounds present in algae and cyanobacteria need to be explored to find the effective therapy for SARS-CoV-2. The present review discusses about the therapeutic potential of such compounds in details but to begin with, the classification and virology of SARS-CoV-2, its pathogenesis and associated symptoms of COVID-19 have been also briefly explained.

SARS CoV-2: virus behind the pandemic

Classification and nomenclature

The Coronaviridae Study Group (CSG) of the International Committee on Taxonomy of Viruses has placed the virus within the Coronaviridae and provisionally named it as 2019-nCoV [8] [Table 1]. The external subdomain of the 2019-nCoV receptor-binding domain (RBD) share similarity with SARS and is closer to bat-SLCoVZXC21 and bat-SL-CoVZC45 at the whole-genome level. Since 2019-nCoV forms a sister clade to the prototype human and bat SARS-CoVs therefore it has been renamed as SARS-CoV-2 [9].

Table 1 Classification of SARS-CoV-2.

Realm	Riboviria
Order	Nidovirales
Sub-order	Cornidovirineae
Family	Coronaviridae
Sub-family	Coronavirinae
Genus	*Betacoronavirus*
Sub-genus	*Sarbecovirus*
Species	Severe acute respiratory syndrome-related coronavirus
Lineage	Lineage B

Virology and pathogenesis of SARS-CoV-2

SARS-CoV-2 is highly stable in the environment and can survive for at least 2–4 days in stool and on dry surfaces at room temperature [10]. It is an enveloped positive sense ss-RNA virus with genome size of approximately 30 kb that encodes structural, non-structural and accessory proteins [Table 2] [11].

Structural proteins include spike (S), envelope (E), membrane (M) and nucleocapsid (N) protein [Fig. 2]. The surface S-glycoprotein assures appropriate interactions between the virus and the host receptor during viral entry. The recombinant receptor binding domain (RBD) of S-protein specifically binds to ACE2 protein, mediates host cell invasion and initiates pathogenesis [12]. The binding efficiency is about 10–20 times higher in SARS-CoV-2 that results in its higher transmissibility and contagiousness. The other three structural proteins help in viral assembly.

Non-structural proteins include 3-chymotrypsin-like protease (3CLpro), papain-like protease (PLpro), helicase, and RNA-dependent RNA polymerase (RdRp) that play an important role in the viral life cycle [Table 3]. The virus releases its genome as ss-positive RNA that subsequently gets translated into polyproteins by the host cell translation machinery [13] [Fig. 3].

Table 2 Details about SARS-CoV-2 genome organization [13].

Region	Nucleotide length	Protein Formed
5′ UTR	265	Non-coding region
ORF 1 ab gene	21290	ORF 1 ab poly-protein
S gene	3822	Spike glycoprotein
ORF 3a gene	828	ORF 3a protein
E gene	228	Envelope protein
M gene	669	Membrane protein
ORF 6a gene	186	ORF 6a protein
ORF 7a gene	366	ORF 7a protein
ORF 7b gene	132	ORF 7b protein
ORF 8a gene	193	ORF 8a protein
N gene	908	Nucleocapsid protein
ORF 10 gene	117	ORF 10 protein
3′ UTR	229	Non-coding region

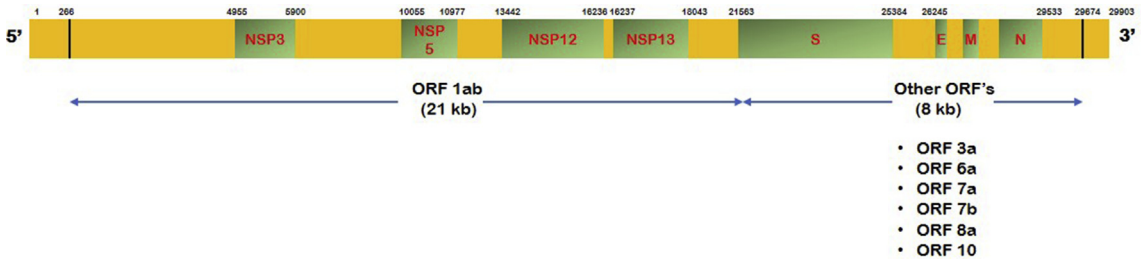

Fig. 2 Gene organization of SARS-CoV-2 virus.

The pathogenesis starts with evading the innate antiviral response, then, embracing the host metabolic apparatus, replicating proficiently inside host cell and consequently inducing cytolysis [14]. Acute respiratory distress syndrome (ARDS) is the common immuno-pathological event for the coronavirus infection and the principal cause of COVID-19 deaths. The main mechanism involved in ARDS is the cytokine storm syndrome (CSS) which is the deadly hysterical systemic inflammatory response generated in response to the release of massive pro-inflammatory cytokines [TNF-α, TGFβ, IFN-(α, γ), IL-(1β, 6, 8, 9 etc.)] and chemokines [CCL-(2, 3 and 5), CXCL-(8, 9 etc.)] by immune effector cells [15]. The immune system consequently triggers a vicious attack on the body by causing acute lung injury (ALI), cardiac injury, RNAaemia, sepsis and multiple organ failure [16].

Prominent symptoms of COVID-19

SARS-CoV-2 attacks the respiratory system, gastrointestinal system, central nervous system, kidney, heart and liver leading to multiple organ failure [4]. The general COVID-19 symptoms include mostly the upper respiratory infection, onset of fever, dry cough, myalgia, fatigue, dyspnea, abnormal leukocyte counts, increased amount of lactate dehydrogenase (LDH) and C-reactive protein (CRP) [10]. Additionally, some patients might also suffer from diarrhoea, vomiting, nausea, headache, dizziness and abdominal pain. The disease when severely progresses causes sepsis, sudden cardiac arrest, pneumonia with ARDS or ALI [11].

Therapeutical approach against COVID-19 till date

The strategies being used in the drug development focusses on two aspects i.e. modulating the host defense system and targeting infectivity of virus. The former method involves blocking the signal transduction pathways in human cells that aids viral replication. The latter targets SARS-CoV-2 itself by inhibiting its RNA synthesis, replication (through acting on critical viral enzymes and blocking the virus binding to human cell receptors) or inhibiting it's self-assembly. The most reliable therapy being used till date is remdesivir which has shown potent *in vitro* activity against SARS-CoV-2, but it is not US Food and Drug Administration (US FDA) approved. Chloroquine has also shown good activity *in vitro* but the cardiovascular toxicity concerns limit its use. Existing clinical proofs support the administration of "Angiotensin Receptor Blockers (ARB)" or ACE inhibitors in patients with COVID-19. However, the fear of development of the drug-resistant form creates a void in between the disease and its therapy. Moreover, reports from randomized clinical trials also hints that the available therapy fails to improve the condition of suspected or confirmed COVID-19 patients.

Thus, exploration of natural sources in perspective of producing new pharmaceutical tools and development of a broad-spectrum class of effective antiviral agent(s) against SARS-CoV-2 is an urgent need [17]. Algal-derived polysaccharides and lectins serve as potential antiviral agents. Herein, bioactivity of some important polysaccharides and lectins including carrageenan, galactans, nostoflan, cyanovirin, microvirin have been explained.

Antiviral activity of algal-derived polysaccharides

Algal polysaccharides are natural polymers that are nontoxic, cheap, biodegradable and biocompatible. They have been

Table 3 Proteins coded by SARS-CoV-2.

Region	Type of Protein	Protein	Functions
NSP 3		Papain like protease (PLPro)	• Proteolysis • INF Antagonist • Deubiquitination
NSP 5		3CL-protease (3CLPro)	• Proteolysis
NSP 12	Non-structural Proteins	RNA dependent Polymerase (RdRp)	• Viral replication and transcription
NSP 13		Helicase	• Viral replication
S		Spike protein	• Virus cell receptor binding
E	Structural Proteins	Envelope protein	• Virion Assembly
M		Membrane protein	
N		Nucleocapsid	

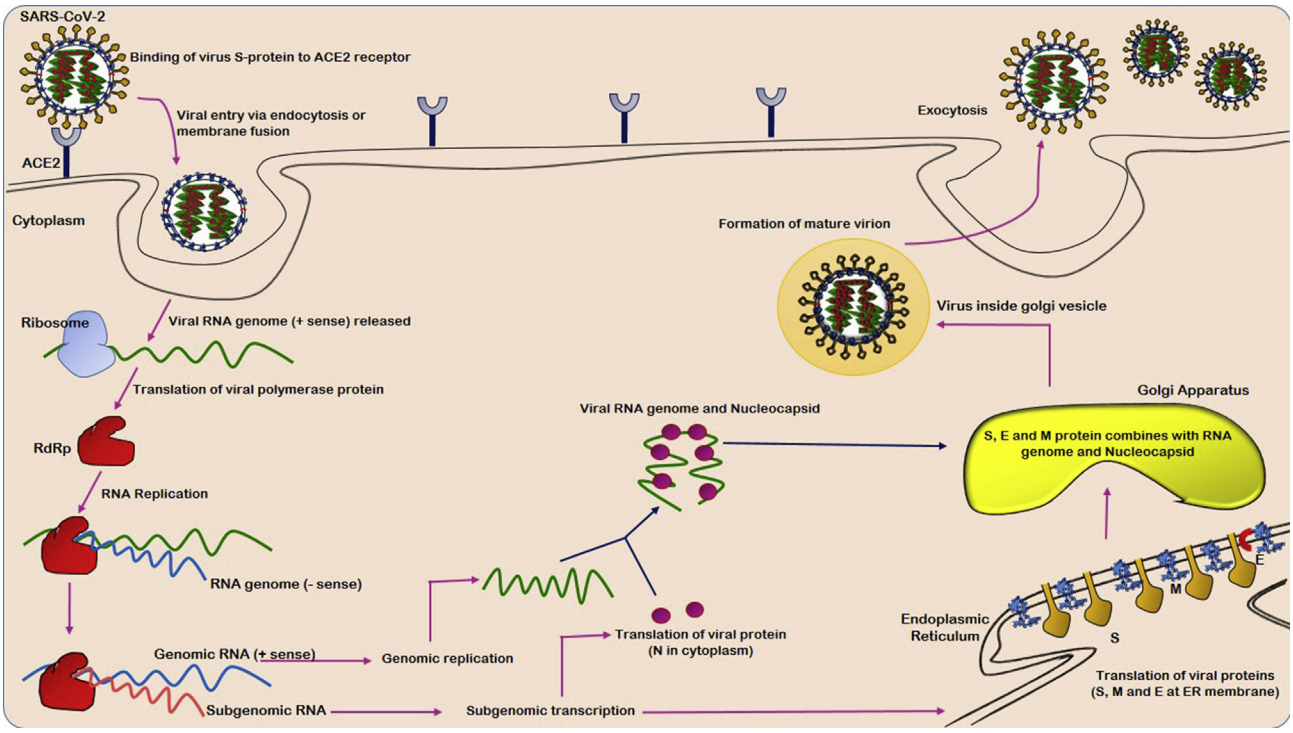

Fig. 3 Pathogenesis mechanism of SARS-CoV-2.

tested for their antiviral efficacy against many viruses including human immunodeficiency virus (HIV), dengue virus (DENV) etc. Thus, they have acquired importance in biomedical and pharmaceutical industries that can be further explored to develop drug molecules targeting SARS-CoV-2 [18].

Carrageenan

A sulphated polymer obtained from red algae such as *Chondrus, Gigartina, Hypnea* and *Eucheuma* that obstructs the entry of viruses by inhibiting their binding or incorporation into the host cells [19–21]. It hinders the replication of dengue virus in mosquito and mammalian cells. They are effective against a range of sexually transmitted human papillomavirus (HPV) that leads to cervical cancer and genital warts. In vivo studies have revealed that low molecular weight carrageenans (3, 5 and 10 kDa) exhibit considerable inhibitory effects against influenza virus [20,22]. The administration of a carrageenan nasal spray (Iota-carrageenan) also known as "super-shedders" increased viral clearance, reduced the duration of common cold disease and relapses and has proved to be an effective treatment of the common cold [23,24]. Kwon et al. [25] have reported that sulfated polysaccharides bind tightly to the S-protein of SARS-CoV-2 which suggests that they can act as decoys to interfere with S-protein binding to the heparan sulfate co-receptor in host tissues inhibiting viral infection. Sulfated polysaccharides from *Porphyridium* have been used as a coating material on the sanitary items and for the production of antiviral drugs [26]. Exopolysaccharides from *Porphyridium* along with carrageenan and sulfated polysaccharides inhibits the internalization or binding of virus on the host cells. Therefore, they reduce COVID-19 proliferation and can prove to be a promising antiviral agent against respiratory viruses belonging to the coronavirus's family [27]. Recently, it has also been confirmed that iota-carrageenan is capable of inhibiting SARS-CoV-2 infection in Vero cell cultures (isolated from kidney epithelial cells extracted from African green monkey) [28].

Alginates

The natural polymers that contain linear copolymers of β-(1–4) linked D-mannuronic acid and β-(1–4) linked L-guluronic acid units, derived from brown algae like *Laminaria hyperborea*, *Laminaria digitata*, *Laminaria japonica*, *Ascophyllum nodosum*, and *Macrocystis pyrifera* [29]. Marine polysaccharide drug 911 derived from alginate significantly inhibit the acute infection of MT4 cells and the chronic infection of H9 cells with HIV-1 [30]. The drug inhibits the viral replication of HIV via significantly decrementing the activity of reverse transcriptase (RTase), discontinuing the virus adsorption, and improving the defense mechanisms of the host cells and inhibiting the virus replication by suppressing the activity of DNA polymerase activity [31–33]. The sulfated form of alginate i.e. sulphated polymannuroguluronate (SPMG) inhibits HIV-1 infection through attachment of virus glycoprotein, gp120 with CD4 molecules on the surface of T-cells. It further blocks the virus replication and the syncytium formation between uninfected and infected cells [34].

Galactans

Red algae *Agardhiella tenera* produces extracellular polysaccharides with linear chains of galactoses that exhibit

antiviral potency against enveloped viruses including herpes simplex virus-1 and -2 (HSV-1 and HSV-2), DENV, HIV-1 and HIV-2, and hepatitis A virus (Hep A) virus. Like alginates, they also block the replication of the virus and the syncytium formation between uninfected and infected cells [35]. Three galactans polysaccharide fractions isolated from marine alga *Callophyllis variegate* have shown activity against HSV-1, HSV-2 and DENV-2 with considerable inhibitory effects along with low cytotoxicity [36]. The sulphated galactan isolated from *Schizymenia binderi* have been found to active against HSV-1 and HSV-2 with lowest cytotoxicity [37]. It has been reported that D, L-galactan hybrid C2S-3, extracted from the Brazilian marine alga *Cryptonemia crenulata* inhibits the multiplication of DENV-2 in Vero cell line [38]. Furthermore, it blocks the replication of HIV-1 and the syncytium formation between uninfected and infected cells as well [39].

Fucans

They are strong anionic high molecular weight polysaccharides found in brown algae. They have been classified into three major groups: glycuronogalacto fucans, fucoidans and xylofuco glycuronans. Sulphated fucans of brown seaweed species *Dictyota mertensii*, *Lobophora variegata*, *Fucus vesiculosus*, and *Spatoglossum schroederi* have been found to prevent HIV infection by blocking the activity of reverse transcriptase [40]. The fucan polysaccharide isolated from *Cladosiphon okamuranus* inhibits DENV-2 infection in baby hamster kidney cell (BHK-21) cell line [41]. The anti-influenza virus compound named MC26 (a new type of fucose polysaccharides), isolated from marine brown algae, *Sargassum piluliferum*, exhibited a stronger anti-influenza virus activity with low cytotoxicity *in vivo* and *in vitro* as compared to the known active compounds [42]. Fucoidans isolated from several algal species such as *Adenocytis utricularis*, *Undaria pinnatifida*, *Stoechospermum marginatum* and *Cystoseira indica*, possesses both *in vivo* as well as *in vitro* antiviral potential against many RNA and DNA viruses like HSV-1 and HSV-2, dengue virus, and cytomegalovirus [43]. They block interaction of virus with the cells and inhibit syncytium formation [44].

Nostoflan

It is the acidic polysaccharide isolated from blue-green algae *Nostoc flagelliforme* [45] and possess antiviral activity against viruses having carbohydrates as cellular receptors. It exhibits potent antiviral activity against HSV-1, HSV-2, human cytomegalovirus and influenza A virus. It inhibits the initial stage of virus infection including the virus binding and internalization processes [46].

Calcium spirulan (Ca-SP)

It has been isolated from the hot water extract of *Spirulina platensis* that exhibits promising antiviral activity against HSV-1, HIV-1 and HSP-1. It inhibits the virus entry into the host cells and syncytium formation even at low concentrations [47].

Naviculan

A sulphated polysaccharide isolated from *Navicula directa* that is composed of galactose, xylose, rhamnose, fucose, mannose and sulphate [48]. It has shown novel antiviral activities against HSV-1, HSV-2 and influenza A virus. It inhibits fusion between the cells that express CD4 receptor and HIV gp160-expressing HeLa cell line [49].

A1 and A2 polysaccharide

The extracellular sulphated polysaccharides isolated from marine microalga *Cochlodinium polykrikoides* that inhibit influenza type-A and type-B virus in MDCK cells, respiratory virus types-A and B in Hep-2 cells, immunodeficiency virus type-1 in MT-4 cells. Inhibition of viral activity is suggested by its potential to reduce blood coagulation [50].

Laminarin

Brown seaweeds like Laminaria japonica, Ecklonia kurome, Eisenia bicyclis produce two types of laminarin i.e. one made of glucose residues while the other terminated by D-mannitol residues [51]. Both possess great antiviral activity and are biocompatible. It prevents adsorption of HIV reverse transcriptase [52].

p-KG03

The sulphated exo-polysaccharide p-KG03, produced by marine microalga *Gyrodinium impudicum*, exhibits unique antiviral activity against encephalomyocarditis virus (EMCV) without showing any toxic effects on HeLa cells. In addition, p-KG03 also inhibit influenza A virus replication by targeting mainly the viral adsorption and incorporation steps [53,54].

Sea algae extract (SAE)

A member of carrageenan isolated from *Schizymenia pacifica* (red algae) that impedes the function and replication of reverse transcriptase in avian retrovirus (avian myeloblastosis virus) and mammalian retrovirus (Rauscher murine leukemia virus) [55,56].

Antiviral activity of algal-derived lectins

Lectins are the class of proteins that bind reversibly to viral receptors in non-covalent and highly specific manner. They counteract several viruses including HIV which makes them possible drug for drug development [57].

Cyanovirin

Lectin isolated from *Nostoc ellipsosporum* that consist of 101 amino acids and has a molecular weight of 11 kDa. It efficiently binds to the envelope glycoprotein (gp120) and inhibit many viruses including HIV-1, HIV-2, simian immunodeficiency virus (SIV) and feline immunodeficiency virus [58].

Cyanovirin acts once the virus-cell attachment is complete or after CD-4 binding step in the entry process [59,60].

Microvirin

Microcystis aeruginosa produces microvirin which is composed of 108 amino acids and is more than 50-fold less toxin than cyanovirin. It does not increase the level of activation markers such as CD25, CD69 and HLA-DR in $CD4^+$ T lymphocytes [61]. It inhibits syncytium formation between HIV-1 infected T cells and uninfected $CD4^+$ T cells.

Griffithsin

The lectin isolated from marine red algae *Griffithsia* sp. and is considered to be the most considerable HIV inhibitor till date [62]. It is made up of 120 amino acids and shows anti-HIV activity with IC_{50} in the picomolar (pm) range. Griffithsin binds to the HIV envelope protein gp120 and inhibits viral infection [63,64]. It is also known to inhibit hepatitis C Virus (HCV) infection of mice having human primary hepatocytes in the liver and prevents *in vitro* HCV infection of Huh-7 hepatoma cells [65]. It binds to the HCV envelope glycoproteins (E1 and E2) and block entry of virus into human hepatocytes [66,67]. Moreover, it has been further observed that griffithsin protects mice infected with genital HSV-2 as well and prevent cell-to-cell spread with no significant adverse effects [68].

Griffithsin is also known to prevent SARS-CoV infection through specific binding to the S-protein. These inhibitory effects gets accompanied with a specific inhibition of deleterious host immune reactions in response to SARS [69]. MERS-CoV gets inhibited at the entry level by griffithsin to prevent infection *in vitro* [70].

Scytovirin

Scytonema varium produces a 95-amino-acid lectin called scytovirin that is active against multiple viruses, including HIV, Zaire ebolavirus, Marburg virus, and SARS-CoV [71,72]. Subcutaneous administration of scytovirin (30 mg/kg/day) for every 6 h to the ebola virus infected mice resulted in survival of 9 out of 10 animals [73]. Scytovirin binds with high affinity to mannose-rich oligosaccharides on the envelope glycoprotein, blocking entry into target cells.

Other lectins (KAA-2, BCA)

Red algae *Kappaphycus alvarezii* and green alga *Boodlea coacta* synthesizes high mannose-specific lectin, KAA and agglutinin, BCA respectively that inhibit infection of multiple influenza strains like the pandemic H1N1-2009. They interfere with the viral entry into host cells upon direct binding of hemagglutinin (HA) on the viral envelope [74,75].

Allophycocyanin

Blue green algae S. *platensis* allophycocyanin neutralizes enterovirus 71-induced cytopathic effect in human rhabdomyosarcoma cells and African green monkey kidney cells. It delay viral RNA synthesis and subside the apoptotic process along-with DNA fragmentation, decrease in membrane damage and declining cell sub-G1 phase [76].

Pheophorbide like compounds

Ethanolic extract of the marine green algae *Dunaliella primolecta* contain pheophorbide like compounds that inhibit cytopathic effect of HSV-1 during its adsorption and invasion into the host cells [77].

Phlorotannins (6,6′-bieckol)

Ecklonia cava produces phlorotannins that inhibit syncytia formation, lytic effects and viral p24 antigen production both *in vitro* and *in vivo* [78]. It has shown potent inhibition of HIV-1 reverse transcriptase enzyme [79].

Conclusions

Novel infectious diseases resulting from RNA viruses will continue to be a serious global health threat. Despite two former major outbreaks of coronavirus infections i.e. the SARS and MERS, the world is still underprepared to effectively manage the current COVID-19 pandemic outbreak. A rigorous effort to develop effective drugs and vaccines against existing and potential future coronavirus infections and other highly pathogenic virus outbreaks is essential to reduce devastating impacts on human life and global healthcare systems. Clinical drug development is too costly and a strenuous process, so there is a need to develop relatively broad-spectrum natural antiviral drugs. Algae and cyanobacteria are the fruitful reservoir of many metabolites like sulfated polysaccharides, lectins, etc. that possess strong antiviral activities and immunity boosting effects. Therefore, these natural resources should be screened thoroughly as there is enormous probability of getting novel compounds that can inhibit SARS-CoV-2.

Success stories

Till date, there are two scientific groups actively involved in developing algae-based edible vaccines for SARS-CoV-2. The first group belong to the Laboratory of Photosynthesis and Bioenergy of the Department of Biotechnology at the University of Verona, Italy. They have adopted two approaches i.e. nuclear transgenesis and chloroplast transformation to introduce a DNA sequence corresponding to the receptor-binding domain of SARS-CoV-2 S-protein in single-celled alga *Chlamydomonas reinhardtii* that resulted in production of antibodies. The algae has been lyophilized and encapsulated to develop an oral vaccine against SARS-CoV-2 [80].

Similar work has been done by the Biotech Company, TransAlgae. They also genetically modified algae, *C. reinhardtii* to produce oral vaccine for SARS-CoV-2. If contamination is prevented then it is possible to accumulate up to 1 mg of the recombinant antigen for each gram of biomass of dried algae. Subsequently, the dehydrated/lyophilized algae can be encapsulated to generate an "oral vaccine." The cell wall from

the dry algae protects the antigens from the harsh acidic and protease-rich gastric environment, enabling the bioactive molecule to reach the intestinal immune system where it can stimulate cellular and humoral responses, hopefully, leading to effective immunization [81].

Future scope

Prevention is better than cure hence the fight against novel coronavirus needs immediate and well-planned strategies. The governments can supply raw algae powders/capsules to improve immunity of individuals that will prevent the viral infection. It is worth mentioning that the recombinant antigen obtained from genetically modified algae can prove to be a boon as it can be dried out and used directly, saving the cost incurred on extraction and purification. Further, the algal cell wall protects the antigen for longer periods without any loss in its efficacy. This will certainly help developing countries that face the problem of storage and transportation of vaccines. Genetic modification of algae will make the vaccine development easy but further research is needed to develop strategies that can inhibit the recurrence of these viral diseases.

Funding

R. Ahmad sincerely thanks University Grants Commission (F.No. 61–1/2019 (SA-III)) for Maulana Azad National Fellowship (MANF-JRF).

Author contributions

All authors have contributed to the manuscript. All authors have revised, edited and approved the final manuscript.

Conflicts of interest

The authors declare no conflict of interest. No conflicts, informed consent, or human or animal rights are applicable to this study.

Acknowledgements

R. Ahmad sincerely thanks University Grants Commission (F.No. 61-1/2019 (SA-III)) for Maulana Azad National Fellowship (MANF-JRF).

REFERENCES

[1] De Wit E, Van Doremalen N, Falzarano D, Munster VJ. SARS and MERS: recent insights into emerging coronaviruses. Nat Rev Microbiol 2016;14:523–34.
[2] Tang B, Bragazzi NL, Li Q, Tang S, Xiao Y, Wu J. An updated estimation of the risk of transmission of the novel coronavirus (2019-nCov). Infectious Disease Modelling 2020;5:248–55.
[3] World Health Organization. Naming the coronavirus disease (COVID-19) and the virus that causes it. 2020. https://www.canaryhealthtech.com/news/naming-the-coronavirus-disease-covid-2019-and-the-virus-that-causes-it. [accessed 25 June 2020].
[4] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med 2020;382:727–33.
[5] Carossino M, Thiry E, de la Grandière A, Barrandeguy ME. Novel vaccination approaches against equine alphavirus encephalitides. Vaccine 2014;3:311–9.
[6] Lu RP, 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;395:565–74.
[7] Deig EF, Ehresmann DW, Hatch MT, Riedlinger DJ. Inhibition of herpesvirus replication by marine algae extracts. Antimicrob Agents Chemother 1974;6:524–5.
[8] Wu A, Peng Y, Huang B, Ding X, Wang X, Niu P, et al. Genome composition and divergence of the novel coronavirus (2019-nCoV) originating in China. Cell Host Microbe 2020;27:325–8.
[9] Gorbalenya AE, Baker SC, Baric RS, de Groo RJ, Drosten C, Gulyaeva AA, et al. The species severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020;5:536–44.
[10] Chen N, Zhou M, Dong X, Qu J, Gong F, Han Y, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020;395:507–13.
[11] Wang C, Horby PW, Hayden FG, Gao GF. A novel coronavirus outbreak of global health concern. Lancet 2020;395:470–3.
[12] Rabenau HF, Cinatl J, Morgenstern B, Bauer G, Preiser W, Doerr HW. Stability and inactivation of SARS coronavirus. Med Microbiol Immunol 2005;194:1–6.
[13] Khailany RA, Safdar M, Ozaslan M. Genomic characterization of a novel SARS-CoV-2. Gene Rep 2020;19:100682.
[14] Du L, He Y, Zhou Y, Liu S, Zheng BJ, Jiang S. The spike protein of SARS-CoV—a target for vaccine and therapeutic development. Nat Rev Microbiol 2009;7:226–36.
[15] Hoffmann M, Weber HK, Schroeder S, Kruger N, Herrler T, Erichsen S, et al. SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 2020;181:1–10.
[16] Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 2020;395:1054–62.
[17] Shi Y, Wang Y, Shao C, Huang J, Gan J, Huang X, et al. COVID-19 infection: the perspectives on immune responses. Cell Death Differ 2020;27:1451–4.
[18] Guo JH, Skinner GW, Harcum WW, Barnum PE. Pharmaceutical applications of naturally occurring water-soluble polymers. Pharmaceut Sci Technol Today 1998;1:254–61.
[19] Lahaye M. Developments on gelling algal galactans, their structure and physico-chemistry. J Appl Phycol 2001;13:173–84.
[20] Grassauer A, Weinmuellner R, Meier C, Pretsch A, Prieschl-Grassauer E, Unger H. Iota-Carrageenan is a potent inhibitor of rhinovirus infection. Virol J 2008;5:107.
[21] Hilliou L, Larotonda FD, Abreu P, Ramos AM, Sereno AM, Gonçalves MP. Effect of extraction parameters on the chemical structure and gel properties of κ/ι-hybrid carrageenans obtained from *Mastocarpus stellatus*. Biomol Eng 2006;23:201–8.

[22] Zeitlin L, Whaley KJ, Hegarty TA, Moench TR, Cone RA. Tests of vaginal microbicides in the mouse genital herpes model. Contraception 1997;56:329–35.
[23] Eccles R, Meier C, Jawad M, Weinmullner R, Grassauer A, Prieschl-Grassauer E. Efficacy and safety of an antiviral iota-carrageenan nasal spray: a randomized, double-blind, placebo controlled exploratory study in volunteers with early symptoms of the common cold. Respir Res 2010;16:1–11.
[24] Koenighofer M, Lion T, Bodenteich A, Prieschl-Grassauer E, Grassauer A, Unger H, et al. Carrageenan nasal spray in virus confirmed common cold: individual patient data analysis of two randomized controlled trials. Multidiscip Respir Med 2014;9:1–12.
[25] Kwon PS, Oh H, Kwon SJ, Jin W, Zhang F, Fraser K, et al. Sulfated polysaccharides effectively inhibit SARS-CoV-2 in vitro. Cell Discov 2020;6:1–4.
[26] Ramus J. Cell surface polysaccharides of the red alga *Porphyridium*. In: Loewus F, editor. Biogenesis of plant cell wall polysaccharides. New York: Academic Press; 1973. p. 333–59.
[27] Nagle V, Gaikwad M, Pawar Y, Dasgupta S. Marine red alga *Porphyridium* sp. as a source of sulfated polysaccharides (SPs) for combating against COVID-19. 2020. [Preprints] 2020040168. Available from: https://www.google.com.tw/url?sa=t&rct=j&q=&esrc=s&source=web&cd=&ved=2ahUKEwjeu7ia-dnuAhUUyYsBHbe7D3QQFjADegQIARAC&url=https%3A%2F%2Fwww.preprints.org%2Fmanuscript%2F202004.0168%2Fv1%2Fdownload&usg=AOvVaw0mip2oHJATrTtfNZ7hKuJ2.
[28] Bansal S, Jonsson CB, Taylor SL, Figueroa JM, Dugour AV, Palacios C, et al. Iota-carrageenan and Xylitol inhibit SARS-CoV-2 in cell culture. 2020. bioRxiv 2020.08.19.225854 [Preprint]. Available from: doi: https://doi.org/10.1101/2020.08.19.225854.
[29] Mabeau S, Kloareg B. Isolation and analysis of the cell walls of brown algae: *Fucus spiralis, F. ceranoides, F. vesiculosus, F. serratus, Bifurcaria bifurcata* and *Laminaria digitate*. J Exp Bot 1987;38:1573–80.
[30] Xianliang X, Hua D, Meiyu G, Pingfang L, Yingxia L, Huashi G. Studies of the anti-AIDS effects of marine polysaccharide drug 911 and its related mechanisms of action. Chin J Mar Drugs 2000;19:4–8.
[31] Xin X, Geng M, Guan H, Li Z. Study on the mechanism of inhibitory action of 911 on replication of HIV-1 in vitro. Chin J Mar Drugs 1999;19:15–8.
[32] Xianliang X, Meiyu G, Huashi G, Zelin L. Study on the mechanism of inhibitory action of 911 on replication of HIV-1 in vitro. Chin J Mar Drugs 2000;19:15–22.
[33] Jiang BF, Xu XF, Li L, Yuan W. Study on '911' anti-HBV effect in HepG2 2115 cells culture. Mod Prev Med 2003;30:517–8.
[34] Wang W, Wang SX, Guan HS. The antiviral activities and mechanisms of marine polysaccharides: an overview. Mar Drugs 2012;10:2795–816.
[35] Witvrouw M, Este JA, Mateu MQ, Reymen D, Andrei G, Snoeck R, et al. Activity of a sulfated polysaccharide extracted from the red seaweed *Aghardhiella tenera* against human immunodeficiency virus and other enveloped viruses. Antiviral Chem Chemother 1994;5:297–303.
[36] Rodríguez MC, Merino ER, Pujol CA, Damonte EB, Cerezo AS, Matulewicz MC. Galactans from cystocarpic plants of the red seaweed *Callophyllis variegata (Kallymeniaceae, Gigartinales)*. Carbohydr Res 2005;340:2742–51.
[37] Matsuhiro B, Conte AF, Damonte EB, Kolender AA, Matulewicz MC, Mejías EG, et al. Structural analysis and antiviral activity of a sulfated galactan from the red seaweed *Schizymenia binderi (Gigartinales, Rhodophyta)*. Carbohydr Res 2005;340:2392–402.
[38] Talarico LB, Duarte ME, Zibetti RG, Noseda MD, Damonte EB. An algal-derived DL-galactan hybrid is an efficient preventing agent for in vitro dengue virus infection. Planta Med 2007;73:1464–8.
[39] Bouhlal R, Haslin C, Chermann JC, Colliec-Jouault S, Sinquin C, Simon G, et al. Antiviral activities of sulfated polysaccharides isolated from *Sphaerococcus coronopifolius* (rhodophytha, gigartinales) and *Boergeseniella thuyoides* (rhodophyta, ceramiales). Mar Drugs 2011;9:1187–209.
[40] Queiroz KC, Medeiros VP, Queiroz LS, Abreu LR, Rocha HA, Ferreira CV, et al. Inhibition of reverse transcriptase activity of HIV by polysaccharides of brown algae. Biomed Pharmacother 2008;62:303–7.
[41] McCandless EL, Craigie JS. Sulfated polysaccharides in red and brown algae. Annu Rev Plant Physiol 1979;30:41–53.
[42] Akamatsu E, Shimanaga M, Kamei Y. Isolation of an anti-influenza virus substance, MC26 from a marine brown alga, *Sargassum piluliferum* and its antiviral activity against influenza virus. Coast Bioenviron 2003;1:29–34 [in Japanese].
[43] Hidari KI, Takahashi N, Arihara M, Nagaoka M, Morita K, Suzuki T. Structure and anti-dengue virus activity of sulfated polysaccharide from a marine alga. Biochem Biophys Res Commun 2008;376:91–5.
[44] Hemmingson JA, Falshaw R, Furneaux RH, Thompson K. Structure and antiviral activity of the galactofucan sulfates extracted from *Undaria pinnatifida* (Phaeophyta). J Appl Phycol 2006;18:185–93.
[45] Whitton BA, Potts M. The ecology of cyanobacteria: their diversity in time and space. 1st ed. Netherlands: Springer; 2007.
[46] Kanekiyo K, Hayashi K, Takenaka H, Lee JB, Hayashi T. Anti-herpes simplex virus target of an acidic polysaccharide, nostoflan, from the edible blue-green alga *Nostoc flagelliforme*. Biol Pharm Bull 2007;30:1573–5.
[47] Hayashi T, Hayashi K, Maeda M, Kojima I. Calcium spirulan, an inhibitor of enveloped virus replication, from a blue-green alga *Spirulina platensis*. J Nat Prod 1996;59:83–7.
[48] Kubo Y, Shozen K, Seto Y. Hyaluronidase inhibitory effect in diatom extracts isolated from deep sea water. Deep Ocean Water Res 2002;3:71–6.
[49] Lee JB, Hayashi K, Hirata M, Kuroda E, Suzuki E, Kubo Y, et al. Antiviral sulfated polysaccharide from *Navicula directa*, a diatom collected from deep-sea water in Toyama Bay. Biol Pharm Bull 2006;29:2135–9.
[50] Hasui M, Matsuda M, Okutani K, Shigeta S. In vitro antiviral activities of sulfated polysaccharides from a marine microalga (*Cochlodinium polykrikoides*) against human immunodeficiency virus and other enveloped viruses. Int J Biol Macromol 1995;17:293–7.
[51] Nelson TE, Lewis BA. Separation and characterization of the soluble and insoluble components of insoluble laminaran. Carbohydr Res 1974;33:63–74.
[52] Muto S, Niimura K, Oohara M, Oguchi Y, Matsunaga K, Hirose K, et al. Polysaccharides and antiviral drugs containing the same as active ingredient. U.S. Patent No. 5,089,481. Washington, DC: U.S. Patent and Trademark Office. United States 1992;5:481.
[53] Yim JH, Kim SJ, Ahn SH, Lee CK, Rhie KT, Lee HK. Antiviral effects of sulfated exopolysaccharide from the marine microalga *Gyrodinium impudicum* strain KG03. Mar Biotechnol 2004;6:17–25.
[54] Kim M, Yim JH, Kim SY, Kim HS, Lee WG, Kim SJ, et al. In vitro inhibition of influenza A virus infection by marine microalga-derived sulfated polysaccharide p-KG03. Antivir Res 2012;93:253–9.
[55] Nakashima H, Kido Y, Kobayashi N, Motoki Y, Neushul M, Yamamoto N. Antiretroviral activity in a marine red alga: reverse transcriptase inhibition by an

aqueous extract of *Schizymenia pacifica*. J Canc Res Clin Oncol 1987;113:413–6.
[56] Nakashima HY, Kido Y, Kobayashi N, Motoki Y, Neushul M, Yamamoto N. Purification and characterization of an avian myeloblastosis and human immunodeficiency virus reverse transcriptase inhibitor, sulfated polysaccharides extracted from sea algae. Antimicrob Agents Chemother 1987;31:1524–8.
[57] Yamashita K, Hara-Kuge S, Ohkura T. Intracellular lectins associated with N-linked glycoprotein traffic. Biochim Biophys Acta Gen Subj 1999;1473:147–60.
[58] Mori T, Boyd MR. Cyanovirin-N, a potent human immunodeficiency virus-inactivating protein, blocks both CD4-dependent and CD4-independent binding of soluble gp120 (sgp120) to target cells, inhibits sCD4-induced binding of sgp120 to cell-associated CXCR4, and dissociates bound sgp120 from target cells. Antimicrob Agents Chemother 2001;45:664–72.
[59] Dey B, Lerner DL, Lusso P, Boyd MR, Elder JH, Berger EA. Multiple antiviral activities of cyanovirin-N: blocking of human immunodeficiency virus type 1 gp120 interaction with CD4 and coreceptor and inhibition of diverse enveloped viruses. J Virol 2000;74:4562–9.
[60] Tiwari V, Shukla SY, Shukla D. A sugar binding protein cyanovirin-N blocks herpes simplex virus type-1 entry and cell fusion. Antivir Res 2009;84:67–75.
[61] Shahzad-ul-Hussan S, Gustchina E, Ghirlando R, Clore GM, Bewley CA. Solution structure of the monovalent lectin microvirin in complex with Manα (1–2) Man provides a basis for anti-HIV activity with low toxicity. J Biol Chem 2011;286:20788–96.
[62] Mori T, O'Keefe BR, Sowder RC 2nd, Bringans S, Gardella R, Berg S, et al. Isolation and characterization of griffithsin, a novel HIV-inactivating protein, from the red alga *Griffithsia* sp. J Biol Chem 2005;280:9345–53.
[63] Barton C, Kouokam JC, Lasnik AB, Foreman O, Cambon A, Brock G, et al. Activity of and effect of subcutaneous treatment with the broad-spectrum antiviral lectin griffithsin in two laboratory rodent models. Antimicrob Agents Chemother 2014;58:120–7.
[64] Xue J, Hoorelbeke B, Kagiampakis I, Demeler B, Balzarini J, Li Wang PJ. The griffithsin dimer is required for high-potency inhibition of HIV-1: evidence for manipulation of the structure of gp120 as part of the griffithsin dimer mechanism. Antimicrob Agents Chemother 2013;57:3976–89.
[65] Meuleman P, Albecka A, Belouzard S, Vercauteren K, Verhoye L, Wychowski C, et al. Griffithsin has antiviral activity against hepatitis C virus. Antimicrob Agents Chemother 2011;55:5159–67.
[66] Takebe Y, Saucedo CJ, Lund G, Uenishi R, Hase S, Tsuchiura T, et al. Antiviral lectins from red and blue-green algae show potent in vitro and in vivo activity against hepatitis C virus. PloS One 2013;8:e64449.
[67] Kachko A, Loesgen S, Shahzad-Ul-Hussan S, Tan W, Zubkova I, Takeda K, et al. Inhibition of hepatitis C virus by the cyanobacterial protein *Microcystis viridis* lectin: mechanistic differences between the high mannose specific lectins MVL, CV-N, and GNA. Mol Pharm 2013;10:4590–602.
[68] Nixon B, Stefanidou M, Mesquita PM, Fakioglu E, Segarra T, Rohan L, et al. Griffithsin protects mice from genital herpes by preventing cell-to-cell spread. J Virol 2013;87:6257–69.
[69] O'Keefe BR, Giomarelli B, Barnard DL, Shenoy SR, Chan PK, McMahon JB, et al. Broad-spectrum in vitro activity and in vivo efficacy of the antiviral protein griffithsin against emerging viruses of the family Coronaviridae. J Virol 2010;84:2511–21.
[70] Millet JK, Séron K, Labitt RN, Danneels A, Palmer KE, Whittaker GR, et al. MiddleEast respiratory syndrome coronavirus infection is inhibited by griffithsin. Antivir Res 2016;133:1–8.
[71] Bokesch HR, O'Keefe BR, McKee TC, Pannell LK, Patterson GM, Gardella RS, et al. A potent novel anti-HIV protein from the cultured cyanobacterium *Scytonema varium*. Biochemistry 2003;42:2578–84.
[72] Li Y, Zhang X, Chen G, Wei D, Chen F. Algal lectins for potential prevention of HIV transmission. Curr Med Chem 2008;15:1096–104.
[73] Garrison AR, Giomarelli BG, Lear-Rooney CM, Saucedo CJ, Yellayi S, Krumpe LR, et al. The cyanobacterial lectin scytovirin displays potent in vitro and in vivo activity against Zaire Ebola virus. Antivir Res 2014;112:1–7.
[74] Sato Y, Hirayama M, Morimoto K, Yamamoto N, Okuyama S, Hori K. High mannose-binding lectin with preference for the cluster of α1–2-mannose from the green alga *Boodlea coacta* is a potent entry inhibitor of HIV-1 and influenza viruses. J Biol Chem 2011;286:19446–58.
[75] Pickett E, Brown J, van Schalkwyk M, Hunter A, Edwards K, Edwards S, et al. Access to influenza immunisation services by HIV-positive patients in the UK, Influenza Other Respir Viruses 2018;12:544–6.
[76] Shih SR, Tsai KN, Li YS, Chueh CC, Chan EC. Inhibition of enterovirus 71-induced apoptosis by allophycocyanin isolated from a blue-green alga *Spirulina platensis*. J Med Virol 2003;70:119–25.
[77] Ohta S, Ono F, Shiomi Y, Nakao T, Aozasa O, Nagate T, et al. Anti-herpes simplex virus substances produced by the marine green alga, *Dunaliella primolecta*. J Appl Phycol 1998;10:349–56.
[78] Artan M, Li Y, Karadeniz F, Lee SH, Kim MM, Kim SK. Anti-HIV-1 activity of phloroglucinol derivative, 6, 6′-bieckol, from *Ecklonia cava*. Bioorg Med Chem 2008;16:7921–6.
[79] Wijesekara I, Yoon NY, Kim SK. Phlorotannins from *Ecklonia cava* (Phaeophyceae): biological activities and potential health benefits. Biofactors 2010;36:408–14.
[80] Specht EA, Mayfield SP. Algae-based oral recombinant vaccines. Front Microbiol 2014;5:60.
[81] Gunasekaran B, Gothandam KM. A review on edible vaccines and their prospects. Braz J Med Biol Res 2020;53:e8749.