Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Cytokine and Growth Factor Reviews 53 (2020) 66–70

Contents lists available at ScienceDirect

Cytokine and Growth Factor Reviews

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

COVID-19: Pathogenesis, cytokine storm and therapeutic potential of interferons

ARTICLE INFO

Keywords:
Interferons
Recombinant
Coronavirus
COVID-19
SARS-CoV-2

ABSTRACT

The outbreak of the novel SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) responsible for coronavirus disease 2019 (COVID-19) has developed into an unprecedented global pandemic. Clinical investigations in patients with COVID-19 has shown a strong upregulation of cytokine and interferon production in SARS-CoV2- induced pneumonia, with an associated cytokine storm syndrome. Thus, the identification of existing approved therapies with proven safety profiles to treat hyperinflammation is a critical unmet need in order to reduce COVI-19 associated mortality. To date, no specific therapeutic drugs or vaccines are available to treat COVID-19 patients. This review evaluates several options that have been proposed to control SARS-CoV2 hyperinflammation and cytokine storm, einclouding antiviral drugs, vaccines, small-molecules, monoclonal antibodies, oligonucleotides, peptides, and interferons (IFNs).

1. Covid-19 pathogenesis

COVID-19, caused by the SARS-CoV2 virus, is a potentially fatal disease that represents a major global public health concern. The SARS-CoV2 virus infects the lower respiratory tract and causes pneumonia in humans, with symptoms that appear milder than SARS or MERS infection, but ultimately becomes a lethal disease of hyperinflammation and respiratory dysfunction [1]. bySARS-CoV2 infection and disease can be approximately divided into three phases: I. an asymptomatic phase with or without detectable virus; II. a non-severe symptomatic phase with upper airway involvement; and III. a severe, potentially lethal disease with hypoxia, 'ground glass' infiltrates in the lung, and progression to acute respiratory distress syndrome (ARDS) with high viral load (Fig. 1) [2].

The coronavirus genome encodes four major proteins: spike (S), nucleocapsid (N), membrane (M), and envelope (E). The S protein is responsible for viral entry into target ACEII expressing cells of the body. Approximately 75 percent of the SARS-CoV2 genome is identical to the SARS-CoV genome, and the amino acid residues required for receptor binding are the same between these two viruses; both viruses use the angiotensin converting enzyme 2 (ACE-2) receptor to infect airway epithelial cells and endothelial cells. [3].

ARDS is the main cause of death in COVID-19 disease, and appears to cause similar immunopathogenic features in SARS-CoV and MERS-CoV infections [4]. One of the main features of ARDS is the cytokine storm - an uncontrolled systemic inflammatory response resulting from the release of pro-inflammatory cytokines and chemokines by immune effector cells [5]. High blood levels of cytokines and chemokines have been detected in patients with COVID-19 infection, including: IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA [6]. The ensuing cytokine storm triggers a violent inflammatory immune response that contributes to ARDS, multiple organ failure, and finally death in severe cases of SARS-CoV-2 infection, similar to SARS-CoV and MERS-CoV infections [5]. Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines [4] (Fig. 2) [7]. The direct cause of death from acute COVID-19 involves cytokine storm damage to lungs and multiple organs of the body: heart, kidney and liver, leading to multiple organexhaustion [8,9,11,12].

2. Interferons as a potential therapy for COVID-19

New therapeutic interventions will likely require a long lead time for the development of approved drugs. Thus, in light of the dire need and urgency to identify the treatment and control of COVID-2019, a repurposing of IFNs and other approved drugs is a potential option in drug development for the control of coronavirus infection. The potential drug options for SARS-CoV-2 infection include the use of enzyme inhibitors, nucleosides, host-targeted agents, convalescent plasma and IFNs [13,14]. Interferons (IFN) enhance the immune system in several ways, by exhibiting various biological functions including antiviral, antiproliferative, immunomodulatory and developmental activities [15] (Fig. 3). IFNs employed therapeutically are manufactured using recombinant DNA technology and multiple clinically approved IFNs are available: IFN α-2a (Roferon), IFN α-2b (Intron A), IFN α-n1 (Wellferon), IFN α-n3 (Alferon), IFN α -con 1 (Infergen), IFN β-1a (Rebif), IFN β-1b (Betaferon), IFN β -1a (Avonex), IFN β -1b (Betaseron), IFN α -2a (Pegasys), IFN α -2b (PegIntron), IFN α P-2b (Sylatron), and IFN γ-1b (Acimmune) [18,19].

In a recent study with MERS-CoV infected patients, the combination of Remdesivir and IFNbeta revealed superior antiviral activity, compared to the effect of lopinavir and ritonavir [20]. Treatment of these patients with oral ribavirin and subcutaneous pegylated IFN alpha-2a demonstrated significant improvement in survival, provided that adequate monitoring and assessment was available [21,22]. Remdesivir and IFN beta may likewise prove useful in the treatment of COVID-19 [14–16], particularly since recent clinical trials have demonstrated that Remdesivir shortened the length of time in hospital intensive care for Covid-19 patients.

Earlier studies showed that coronaviruses including MERS, SARS, human coronavirus 229E, and avian infectious bronchitis virus (IBV)

https://doi.org/10.1016/j.cytogfr.2020.05.002
Received 11 April 2020
Available online 07 May 2020

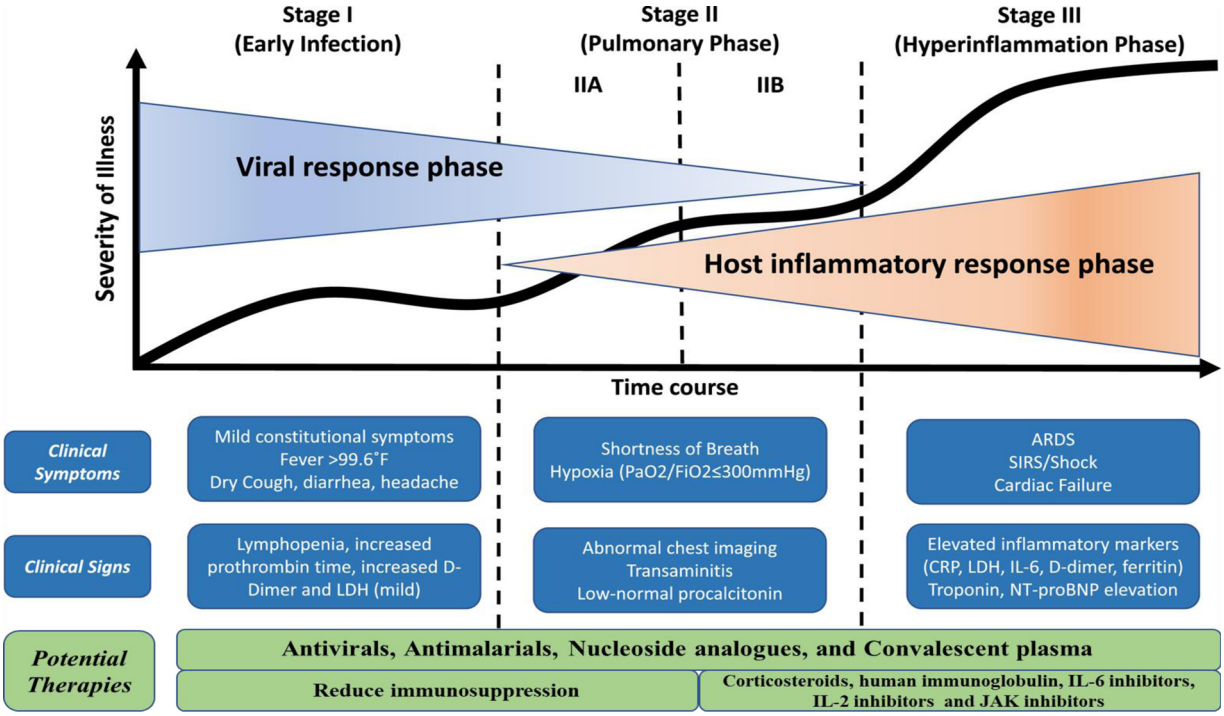

Fig. 1. COVID-19 pathogenic phases and potential therapeutic targets (modified and adopted from Siddiqi and Mehra, 2020 [38]).

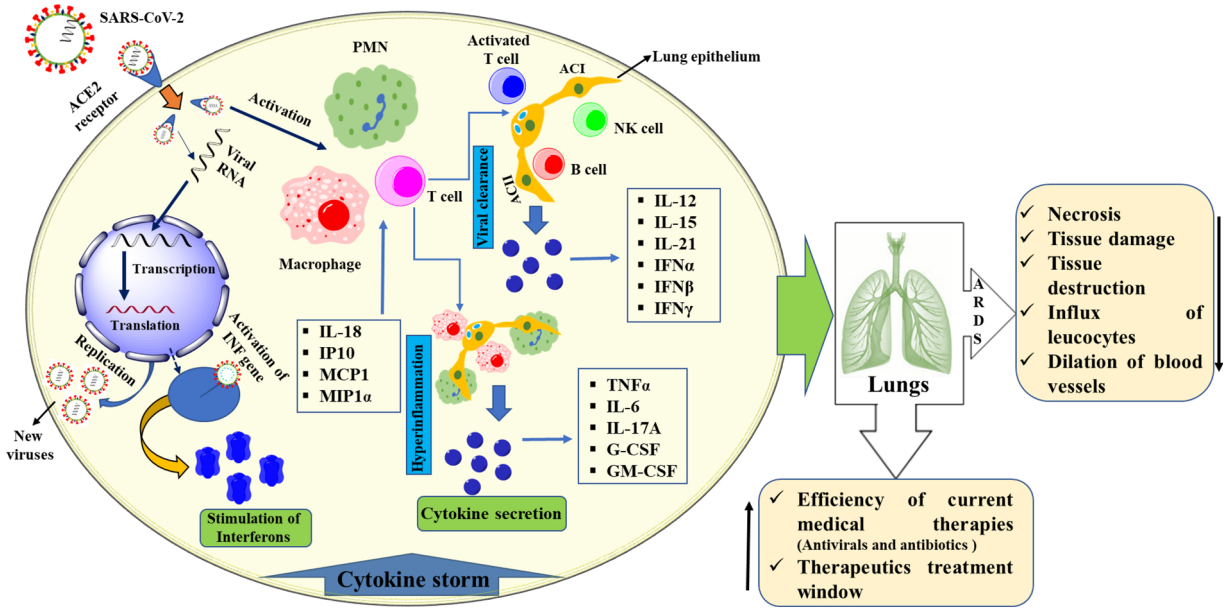

Fig. 2. Schematic representation of COVID-19 pathogenesis and cytokine storm with possible effects. SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; ACE2: angiotensin-converting enzyme 2; PMN: polymorphonuclear granulocyte; AC: alveolar cell; NK: natural killer).

were susceptible to IFN treatment [17,23]. In patients with MERS infection, a combination of ritonavir plus IFN α2a or IFN α-2b resulted in significantly improved survival after 14 days of treatment. The combination of ritonavir and IFNβhad no significant effect on clinical outcome in patients infected with MERS, but the combination of ribavirin (1), ritonavir (2) and IFN α-2a inhibited viremia within 48h of treatment [13]. The use of recombinant IFNs (IFN -α, IFN -β and exogenous IFNs) in the treatment of SARS-CoV2, SARS-CoV and MERS-CoV demonstrated that IFN response inhibited protein synthesis and replication of the virus [24–26]. IFN α and γ, alone or in combination, showed partial efficacy against the animal coronaviruses, as well as inhibiting SARS-CoV replication *in vitro*. IFN β had the highest potency, demonstrating prophylactic protection and antiviral potential post infection [27]. Therefore, it may be worthwhile to test the safety and efficacy of human and recombinant IFNs in SARS-CoV-2-infected patients, alone or in combination with other antiviral drugs.

3. Potential combination approaches for COVID-19

At present, there are no Food and Drug Administration (FDA)-approved drugs specifically indicated for the treatment of patients with COVID-19, with the exception of the recently studied Remdesivir. It was shown that Remdesivir reduced the patients' time in ICU from fifteen days to eleven days. Originally developed as a small molecule

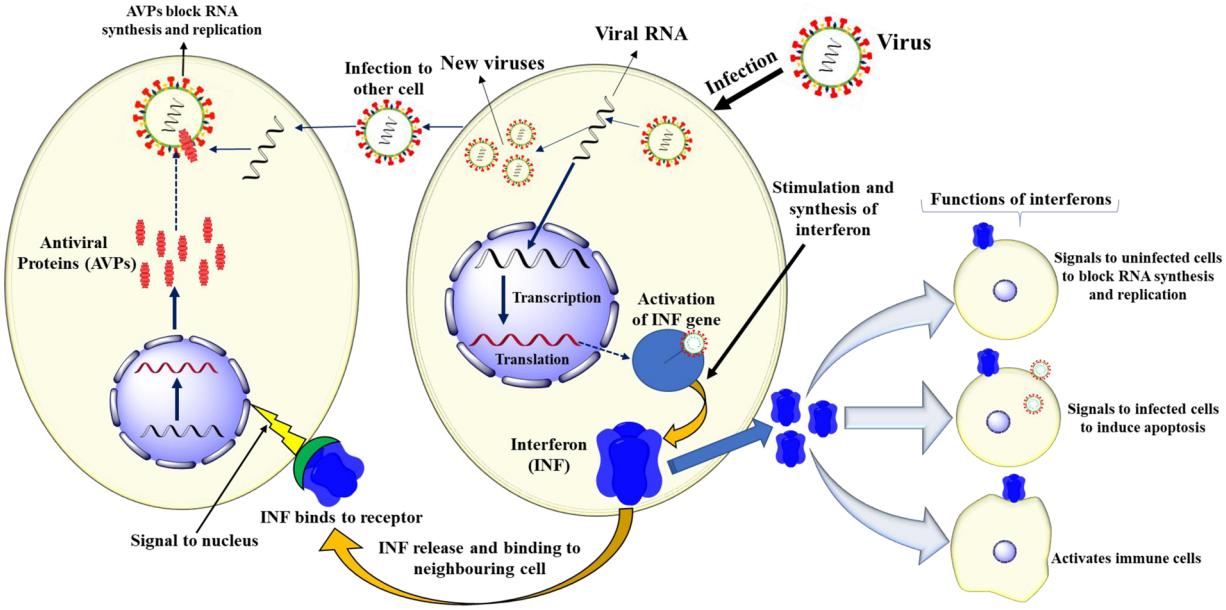

Fig. 3. Mechanism of interferon biosynthesis and their functions.

Table 1
Combinational remedies and drugs as potential targets for COVID-19.

Name of the agent/therapy	Targeted virions infection	Target virion mechanism	References
Thalidomide and Glucocorticoids	SARS-CoV-2	Regulate immunity, inhibit the inflammatory cytokine surg	[30]
Remdesivir and IFNa2	SARS-CoV-2	Improves pulmonary function and reduces lung viral loads	[13]
Chloroquine and Hydroxychloroquine	SARS-CoV-2	attenuation of cytokine production and inhibition of autophagy - shown recently to be ineffective in clinical studies	[31]
Lopinavir and Ritonavir	HIV, MERS-CoV and SARS-CoV-2	Protease inhibitor, inhibits 3CLpro	[13]
Lopinavir, oseltamivir and ritonavir	SARS-CoV-2	Targetiviral protease	[32]
Lopinavir, ritonavir, and interferon beta	MERS-CoV and SARS-CoV-2	Slightly reduced viral load and improved pulmonary function	[20]
Convalescent plasma	SARS-CoV-2, SARS-CoV and MERS-CoV	Inhibited virus entry to the target cells, suppressed viraemia by anti-SARS-CoV2 antibody	[13]
Hydroxychloroquine and Azithromycin	SARS-CoV-2	Viral load reduction through inhibition of replication	[33]
Camostat mesilate Hydroxychloroquine	SARS-CoV-2	Inhibitor of the host cell serine protease and angiotensin receptor blockers	[34]
Darunavir and Umifenovir	SARS-CoV-2	Viral load reduction through inhibition of replication	[35]
Ribavirin and Interferon-α	SARS-CoV-2	Lowered the risk of acute respiratory distress syndrome (ARDS) and death	[36]
Hydroxychloroquine and Nitazoxanide	SARS-CoV-2	Adjuvant therapy in Covid-19	[37]

compound against Ebola virus, Remdesivir acts by inhibiting the viral RNA dependent RNA polymerase. However, it is difficult to imagine how the direct antiviral properties of Remdesivir could be potently active during the immunopathogenic ARDS phase of COVID-19 disease, suggesting that other off-target effects may be attributed to the drug. Further studies, particularly amongst patient populations at earlier stages of the disease, are warranted to resolve these issues.

A number of drugs and combinational therapies have been identified using previously approved drugs that targett clathrin-mediated endocytosis, viral protease, regulate immunity, inhibit the inflammatory cytokine surge, improve pulmonary function and reduce lung viral loads (Table 1). At present, treatment of COVID-19 cytokine storm focuses primarily on support and symptomatic treatment of inflammation, cytokine storm and compromised respiratory function [28]. Recently, a number of specific anti-cytokine approaches have proven effective in the treatment of a variety of cytokine storm syndromes, and include drugs targeting interleukin-1 (IL-1), IL-6, IL-18, and interferon-gamma [29]. While randomized trials will be needed to confirm which, if any, of these therapeutics are effective in Covid-19-infected patients with cytokine storm syndrome, IL-6 blockade using anti-IL6 antibody has recently been reported, with successful outcomes in some individuals [10]. While working to prevent future outbreaks of coronavirus infections with vaccine development and new or re-purposed anti-viral medicines, it remains of utmost importance to use the knowledge at our disposal to treat those patients most at risk of dying from Covid-19-induced cytokine storms.

Declaration of Competing Interest

There are no financial or other interests related to this review that represent a conflict of interest.

Acknowledgements

This work was supported by Zhejiang University special scientific research fund for COVID-19 prevention and control, National Natural Science Fund of China (81522049, 31870135, 31571735), Zhejiang Provincial Wanren Program for Leading Talents of Science and Technology Innovation (2018R52050), Zhejiang Provincial Program for the Cultivation of High-level Innovative Health talents (2018-62-3), the “Dawn” Program of Shanghai Education Commission (16SG38), Shanghai Science and Technology Committee Project (17JC1404300), Opening Project of Zhejiang Provincial Preponderant and Characteristic

Subject of Key University (Traditional Chinese Pharmacology, Zhejiang Chinese Medical University (ZYAOXZD2019001)).

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.cytogfr.2020.05.002.

References

[1] Y. Chen, Q. Liu, D. Guo, Emerging coronaviruses: genome structure, replication, and pathogenesis, J. Med. Virol. 92 (2020) 418–423, https://doi.org/10.1002/jmv.25681.

[2] Y. Shi, Y. Wang, C. Shao, et al., COVID-19 infection: the perspectives on immune responses, Cell Death Differ. 27 (2020) 1451–1454, https://doi.org/10.1038/s41418-020-0530-3.

[3] H. Li, S.M. Liu, X.H. Yu, C.L. Tang, C.K. Tang, Coronavirus disease 2019 (COVID-19): current status and future perspectives, Int. J. Antimicrobial Agents (2020) 105951, https://doi.org/10.1016/j.ijantimicag.2020.105951.

[4] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, et al., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, Lancet 395 (10223) (2020) 497–506, https://doi.org/10.1016/S0140-6736(20)30183-5.

[5] X. Li, M. Geng, Y. Peng, L. Meng, S. Lu, Molecular immune pathogenesis and diagnosis of COVID-19, J. Pharm. Analysis (2020), https://doi.org/10.1016/j.jpha.2020.03.001.

[6] H.A. Rothan, N. Siddappa, S.N. Byrareddy, The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak, J. Autoimmun. 109 (2020) 102433, , https://doi.org/10.1016/j.jaut.2020.102433.

[7] X. Sun, T. Wang, D. Cai, Z. Hu, J. Chen, H. Liao, L. Zhi, H. Wei, Z. Zhang, Y. Qiu, J. Wang, A. Wang, Cytokine storm intervention in the early stages of COVID-19 pneumonia, Cytokine Growth Factor Rev. (2020), https://doi.org/10.1016/j.cytogfr.2020.04.002.

[8] P. Mehta, D.F. McAuley, M. Brown, E. Sanchez, R.S. Tattersall, J.J. Manson, COVID-19: consider cytokine storm syndromes and immunosuppression, Lancet (2020), https://doi.org/10.1016/S0140-6736(20)30628-0.

[9] J.R. Tisoncik, M.J. Korth, C.P. Simmons, J. Farrar, T.R. Martin, M.G. Katze, Into the eye of the cytokine storm, Microbiol. Mol. Biol. Rev. 76 (2012) 16–32, https://doi.org/10.1128/MMBR.05015-11.

[10] B. Liu, M. Li, Z. Zhou, X. Guan, Y. Xiang, Can we use interleukin-6 (IL-6) blockade for coronavirus disease 2019 (COVID-19)-induced cytokine release syndrome (CRS)? J. Autoimmun. (2020), https://doi.org/10.1016/j.jaut.2020.102452 102452.

[11] Y. Wang, X. Chen, W. Cao, Y. Shi, Plasticity of mesenchymal stem cells in immunomodulation: pathological and therapeutic implications, Nat. Immunol. 15 (2014) 1009–1016, https://doi.org/10.1038/ni.3002.

[12] G. Wang, K. Cao, K. Liu, Y. Xue, A.I. Roberts, F. Li, et al., Kynurenic acid, an IDO metabolite, controls TSG-6-mediated immunosuppression of human mesenchymal stem cells, Cell Death Differ. 25 (2018) 1209–1223, https://doi.org/10.1038/s41418-017-0006-2.

[13] G. Li, E. De Clercq, Therapeutic options for the 2019 novel coronavirus (2019-nCoV), Nat. Rev. Drug Discov. 19 (2020) 149–150, https://doi.org/10.1038/d41573-020-00016-0.

[14] T. Pillaiyar, S. Meenakshisundaram, M. Manickam, Recent discovery and development of inhibitors targeting coronaviruses, Drug Discov. Today (2020), https://doi.org/10.1016/j.drudis.2020.01.015.

[15] B.X. Wang, E.N. Fish, Global virus outbreaks: interferons as 1st responders, Semin. Immunol. 43 (2019) 101300, , https://doi.org/10.1016/j.smim.2019.101300.

[16] E. Kindler, V. Thiel, F. Weber, Interaction of SARS and MERS Coronaviruses with the antiviral interferon response, Adv. Virus Res. 96 (2016) 219–243.

[17] Y. Yin, R.G. Wunderink, MERS, SARS and other coronaviruses as causes of pneumonia, Respirology 23 (2018) 130–137, https://doi.org/10.1111/resp.13196.

[18] E.L. Tan, E.E. Ooi, C.Y. Lin, H.C. Tan, A.E.B. Ling, L.W. Stanton, Inhibition of SARS coronavirus infection in vitro with clinically approved antiviral drugs, Emerg. Infect. Dis. 10 (4) (2004) 581–586.

[19] N. Uppangala, Recombinant Interferon as Drugs, https://www.biotecharticles.com/Healthcare-Article/Recombinant-Interferon-as-Drugs-196.html.

[20] T.P. Sheahan, A.C. Sims, S.R. Leist, A. Schafer, J. Won, et al., Comparative therapeutic efficacy of remdesivir and combination lopinavir, ritonavir, and interferon beta against MERS-CoV, Nat. Commun. 11 (2020) 222.

[21] A.S. Omrani, M.M. Saad, K.Baig A. Bahloul, M. Abdul-Matin, A.Y. Alaidaroos, G.A. Almakhlafi, M.M. Albarrak, Z.A. Memish, A.M. Albarrak, Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study, Lancet Infect. Dis. 14 (2014) 1090–1095.

[22] L. Bouadma, F.X. Lescure, J.C. Lucet, Y. Yazdanpanah, J.F. Timsit, Severe SARS-CoV-2 infections: practical considerations and management strategy for intensivists, Intensive Care Med. 46 (2020) 579–582.

[23] L.E. Hensley, L.E. Fritz, P.B. Jahrling, C.L. Karp, J.W. Huggins, T.W. Geisbert, Interferon-beta 1a and SARS coronavirus replication, Emerg. Infect. Dis. 10 (2) (2004) 317–319.

[24] D. Falzarano, E. Wit, A.L. Rasmussen, F. Feldmann, H. Feldmann, Treatment with interferon-α2b and ribavirin improves outcome in MERS-CoV-infected rhesus macaques, Nat. Med. 19 (10) (2013) 1313–1317.

[25] C.C. Li, X.J. Wang, H.R. Wang, Repurposing host-based therapeutics to control coronavirus and influenza virus, Drug Discov. Today 24 (2019) 726–736.

[26] A. Zumla, Chan, E.I. Azhar, D.S.C. Hui, K.Y. Yuen, Coronaviruses -drug discovery and therapeutic options, Nat. Rev. Drug Discov. 15 (2016) 327–347, https://doi.org/10.1038/nrd.2015.37.

[27] J. Cinatl, B. Morgenstern, G. Bauer, P. Chandra, H. Rabenau, H.W. Doerr, Treatment of SARS with human interferons, Lancet 362 (2003) 293–294.

[28] https://www.cusabio.com/COVID-19-Cytokine-Storm. Accessed on 01/05/2020.

[29] Q. Ye, B. Wang, J. Mao, The pathogenesis and treatment of the `Cytokine Storm' in COVID-19, J. Infect. (2020), https://doi.org/10.1016/j.jinf.2020.03.037.

[30] C. Chen, F. Qi, K. Shi, Y. Li, J. Li, Y. Chen, J. Pan, T. Zhou, X. Lin, J. Zhang, Y. Luo, X. Li, J. Xia, Thalidomide combined with low-dose glucocorticoid in the treatment of COVID-19 Pneumonia, Preprints (2020) 2020020395.

[31] J.M. Sanders, M.L. Monogue, T.Z. Jodlowski, J.B. Cutrell, Pharmacologic treatments for coronavirus disease 2019 (COVID-19): a review, JAMA (2020), https://doi.org/10.1001/jama.2020.6019.

[32] M. Muralidharan, R. Sakthivel, D. Velmurugan, M.M. Gromiha, Computational studies of drug repurposing and synergism of lopinavir, oseltamivir and ritonavir binding with SARS-CoV-2 Protease against COVID-19, J. Biomol. Struct. Dyn. (2020), https://doi.org/10.1080/07391102.2020.1752802.

[33] P. Gautret, J.C. Lagier, P. Parola, et al., Hydroxychloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial, Int. J. Antimicrob. Agents (2020), https://doi.org/10.1016/j.ijantimicag.2020.105949.

[34] F. Sanchis-Gomar, C.J. Lavie, C. Perez-Quilis, B.M. Henry, G. Lippi, Angiotensin-converting enzyme 2 and anti-hypertensives (angiotensin receptor blockers and angiotensin converting enzyme inhibitors) in coronavirus disease 2019 (COVID-19), Mayo Clin. Proc. (2020), https://doi.org/10.1016/j.mayocp.2020.03.026.

[35] M. Costanzo, M.A.R. De-Giglio, G.N. Roviello, SARS-CoV-2: Recent Reports on Antiviral therapies based on lopinavir/ritonavir, darunavir/umifenovir, hydroxychloroquine, remdesivir, favipiravir and other drugs for the treatment of the new coronavirus, Curr. Med. Chem. 27 (2020), https://doi.org/10.2174/0929867327666200416131117.

[36] L. Dong, S. Hu, J. Gao, Discovering drugs to treat coronavirus disease 2019 (COVID-19), Drug Discov. Ther. 14 (2020) 58–60, https://doi.org/10.5582/ddt.2020.01012.

[37] K.M. Okasha, Hydroxychloroquine and Nitazoxanide Combination Therapy for COVID-19, (2020) https://clinicaltrials.gov/ct2/show/NCT04361318.

[38] H.K. Siddiqi, M.R. Mehra, COVID-19 illness in native and immunosuppressed states: a clinical-therapeutic staging proposal, J. Heart Lung Transplant. (2020), https://doi.org/10.1016/j.healun.2020.03.012.

Dr. Shivraj Nile obtained M.Sc. in Biotechnology (2004) and PhD in Life Science, SRTM, University, India (2010). He worked as KU-Brain Pool post-doctoral fellow (2012-2014), Konkuk University, He currently working as Associate Professor, Zhejiang Chinese Medical University, China. Previously worked as Assistant Professor, Konkuk University, Korea (2014-2018) and SRTM, University, Nanded (2010-2014). Received RGNF Research Fellowship (UGC, India) (2006-2010). He had 9 years research experience in food science, phytochemistry, biotechnology and nanotechnology. Dr. Nile had more than 85 research publications including Crit. Rev. Food Sci, Nutr, Trends in Food Sci Technol, Nano-Micro Lett, J. Clean Prod, Food Chem, Food Chem Toxicol, Ind Crops Products, Nutrition, Food Res Int, Food Function, Phytomedicine, Frontiers in Pharmacology, and Food Review Int. Also having 3 patents and 6 research projects on his credit and He received 12 national and international research awards. Associate editor for e-Food journal, Combinatorial Chemistry & High Throughput Screening, Journal Recent Patents on Food Nutrition & Agriculture, Current Pharmaceutical Analysis, Journal of Nutrition & Health, Journal of Analytical & Molecular Techniques, International Journal of Recent Trends in Science & Technology, and Journal of Environmental Studies. His expertise is food science, biochemistry, pharmacology, natural products, nanotechnology, and drug discovery. His research mainly focused on functional food, natural colorants, drug development, food nanotechnology and phytomedicine.

Ms. Arti Nile finished her master's degree in Biotechnology (2012), SRTM, University, India. She is having 3 years industrial experience as CRA and CDM. Currently she is perusing her PhD in Food Science, Konkuk University, Korea. Her major research focused on utilization of fruit and crop waste towards bioactive compound extraction and determination of biological activities. She got research fellowship from NRF-Korea for her PhD work and she published more than 10 research papers in various international journals. She is also having good experience with clinical research and data management.

Dr. Jiayin Qiu obtained her PhD in Pharmacology, Southern Medical University, China (2014). She worked as a visiting student in Weizman Institute of Science in Isreal (2012-2014). She currently working as postdoctoral in Zhejiang Chinese Medical University, China. Host Youth Program of National Natural Science Foundation of China (2016-2018) and Natural Science Foundation of Guangdong Province (2015-2017). Dr. Qiu had 19 research publications including J Biol Chem, Frontiers in Pharmacology and Journal of Antimicrobial Chemotherapy etc. Her research mainly focused on Anti-virus Pharmacolo gy.

Prof. Lin Li is a professor of pharmacology of School of Pharmaceutical Sciences, Southern Medical University. She was awarded with "The Outstanding Teacher of Southern Medical University". Prof. Li obtained her PhD in Pharmacology, Southern Medical University, China (2010). In 2012, Prof. Li was trained by David Geffen School of Medicine in University of California for teaching skills. During 2008 to 2010, she worked as a visiting scientist in New York Blood Center. Prof. Li is the director of World Federation of Chinese Medicine Societies, the secretary general of Division of Anti-inflammatory and Immunology of Chinese Pharmacological Society (CPS). Prof. Li mainly engaged in anti-viral drug development and HIV latency research. She was awarded about seven research grants. Prof. Li has already published more than 30 SCI papers in academic journals like J Antimicrob Chemother, J. Acquir. Immune Defic. Syndr., Retrovirology, Antimicrob. Agents Chemother, with a total impact factor over 100.

Prof. Xu Jia obtained his PhD in Biochemistry and Molecular Biology, Fu Dan University, China (2012). He worked as a Professor in Chengdu Medical College since 2012. Received National Natural Science Foundation of China (2013, 2014, 2018) and Sichuan science and technology fund for outstanding youth (2014). He became the head of the research and innovation team of universities in Sichuan province for research on bacterial resistance and anti-infection (2015). Honors he received: outstanding contribution of Sichuan provincial commission of health and family planning (2017), Sichuan thousand talents program (2018), Sichuan academic and technological leader (2018), Sichuan new youth (2019). Prof. Dr. Jia had more than 20 research publications including Cell, Nucleic Acids Research and Frontiers in Microbiology etc. The related results on the mechanism of bacterial resistance were published in the journal Cell. His expertise is on antibiotic resistance, the structure and function of non-coding RNAs, especially riboswitch, SARS-CoV-2, COVID-19, antivirus drugs, bacterial epidemiology, antibacterial drugs and aging.

Prof. Guoyin Kai obtained his PhD in Biochemistry and Molecular Biology, Shanghai Jiaotong University, China (2005). He worked as a visiting scholar in Brookhaven National Laboratory in USA (2012-2013). He currently working as Professor, Zhejiang Chinese Medical University, China. Previously worked as associate Professor (2005-2012) and Professor (2012-2017) in Shanghai Normal University, China (2005-2017). Received Excellent Youth Talent Project from National Science Fund (2016-2018) and Meiji Life Science Award (China) (2014). Prof. Dr. Kai had more than 100 research publications including Metab Eng, Chem Eng J, New Phytol, Nano-Micro Lett, Crit. Rev. Food Sci, Nutr, J Exp Bot, Food Chem, Nanomedicine, Phytomedicine, J. Agr Food Chem, Food Chem Toxicol, and PNAS etc. Also having 17 Chinese patents and 28 research projects as PI and received 14 research awards. His expertise is on biotechnology and bioactive compounds and their biological evaluation. His research mainly focused on natural product, phytomedicine and biotechnology

Shivraj Hariram Nile[a], Arti Nile[a], Jiayin Qiu[a], Lin Li[b], Xu Jia[c,*], Guoyin Kai[a,*]

[a] *Department of Pharmacy, Zhejiang Chinese Medical University, Hangzhou, Zhejiang, 310053, China*

[b] *Guangdong Provincial Key Laboratory of New Drug Screening, Guangzhou Key Laboratory of Drug Research for Emerging Virus Prevention and Treatment, School of Pharmaceutical Sciences, Southern Medical University, Guangzhou, China*

[c] *Non-Coding RNA and Drug Discovery Key Laboratory of Sichuan Province, Chengdu Medical College, Chengdu, 610500, China*

E-mail addresses: jiaxu@cmc.edu.cn (X. Jia), guoyinkai1@126.com (G. Kai).

* Corresponding authors.