EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES
http://www.ejbps.com

ISSN 2349-8870
Volume: 8
Issue: 9
192-197
Year: 2021

INNATE IMMUNE MECHANISMS, TRAINED IMMUNITY, AND IMMUNOTHERAPY DURING SARS-COV-2 INFECTION: A REVIEW OF LITERATURE

***Samina Khan[1], Zainab Imtiaz[2], Cecilia Gadaga[3], Ghulam Muhammad Humayun[4], Blessing Ebong[5], Olusoji Rahman Adesoji[6], Richard Okeke[7], Mujidat Oluwafikayo Hammed[8], Lisandra Vega Cruz[9] Tooba Shaukat Butt[10], Ijeoma Akabalu[11], Odunayo Susan Lawal[12], Iyanu Victoria Olateju[13], Matthew Oluwafemi Owolabi[13] and Ofure Harrison[14]**

[1]Royal Alexandra Hospital, AHS, Canada.
[2]Lahore Medical and Dental College, Pakistan.
[3]Texila American University, Guyana.
[4]Allama Iqbal Medical College, Pakistan.
[5]Uuniversity of calabar, Nigeria.
[6]University of Lagos, Nigeria.
[7]Ivano-Frankivsk National Medical University, Ukraine.
[8]VN Karazin National University, Ukraine.
[9]American University of Antigua, College of Medicine.
[10]United Medical and Dental College, Pakistan.
[11]Caribbean Medical University School of Medicine, Curacao.
[12]University of Arizona, Tucson.
[13]Washington Adventist University, USA.
[14]V. N karazin Kharkiv National University.

***Corresponding Author: Samina Khan**
Royal Alexandra Hospital, AHS, Canada.

Article Received on 12/07/2021 **Article Revised on 01/08/2021** **Article Accepted on 21/08/2021**

ABSTRACT

Introduction: Innate immunity plays a critical role in the host response following SARS-CoV-2 infection. The innate immune mechanism has gained prominence for its aberrant responses, known as cytokine storm syndrome. **Methods:** A thorough search of medical databases was conducted to synthesize information in a tabulated and narrative review. **Results:** Combined with evasive viral responses, innate immunity plays a critical role in the morbidity and mortality related to COVID-19 infection. Trained innate immunity, particularly myeloid cell progeny, is a confounder that needs to be explored further. Vaccinations and endemic infections play a critical role in enhancing trained innate immunity. **Conclusion:** Our findings collate relevant insight into innate immune mechanisms as well as explain the potential role of environmental priming, known as epigenetics, as a contributor to variable innate immunologic responses based on geographic differences.

KEYWORDS: Immunity, immunology, trained immunity, innate immunity, viral evasion, correlates of protection.

INTRODUCTION

Innate immunity is a key component that leads to morbidity and mortality during severe acute respiratory coronavirus-2 (SARS-CoV-2) infections. When the virus enters humans, pattern recognition receptors (PRRs) get activated that are directly associated with pathogen-associated molecular patterns (PAMPs), specific to the SARS-CoV-2 virus.[1] Following this, active recruitment of monocytes and macrophages occurs at the local site, e.g. lungs.[2] The innate immune responses have been noted to direct how the adaptive immunity responds to SARS-CoV-2 infection. Prominent cytokines involved in innate immunological responses such as interleukin-6 (IL-6), interleukin-10 (IL-19) have been reported with SARS-CoV-2 infection.[3] The phenomenon of innate immunity during SARS-CoV-2 infection has been cited as the cytokine storm syndrome (CSS), conferring a poor prognosis.

Notably, there are key differences in the manner by which innate immunity functions. The concept of trained innate immunity was first coined in 2011.[4] This phenomenon is associated with the adaptive characteristics of humans that are part of the natural human defense mechanisms.[5] Endemic infections and vaccinations have been cited to induce trained innate

immunity mechanisms. These characteristics are defined as long-term functional reprogramming of the natural innate immunity which occurs within similar geographical regions. For instance, the Bacillus Calmette-Guerin (BCG) vaccine has been shown to induce varying degrees of trained immunity in the literature.[6,7] The role of epigenetic reprogramming has also been observed as a mediator of trained innate immunity.[5] Typically, trained immunity has been shown to last up to 1 year. However, the transgenerational inheritability of trained immunity has been proven.[8,9] Our review sheds light on the innate immune mechanisms of SARS-CoV-2 infection. We also review current immunotherapy candidates being observed for their efficacy during COVID-19 infection. Further, we also collate information on trained innate immunity and the correlates of protection that it offers based on regional differences.

METHODOLOGY

The following databases were reviewed including Pubmed/MEDLINE, Scopus, and Google Scholar. Only articles in English were reviewed. There were no restrictions on the data search. All articles from inception until June 18, 2021, were reviewed. The keywords used included "immunology", "innate", "COVID-19", "trained innate", and "BCG". There were no exclusion criteria with regards to the type of study. Specific well-known journals were also reviewed including the New England Journal of Medicine, the Journal of the American Medical Association, and the British Medical Journal. Three investigators found relevant studies for inclusion and a fourth investigator solved any discrepancies for the narrative synthesis of data.

Host Innate Immune Responses

Innate immunity is known as the first line of defense against infectious diseases. Three key components of innate immunity include dendritic cells, myeloid cells including monocytes, macrophages, and neutrophils, and natural killer cells.[10] These cells carry specialized receptors known as pathogen recognition receptors (PRRs) which recognize a specific pattern of protein, carbohydrate moiety present on pathogens known as pathogen-associated molecular patterns (PAMPs).[1] The identification of PAMPs by PRRs promotes a cascade of events including transcription of pro-inflammatory cytokine genes regulated by the NF-kB pathway.[1] The activation of macrophages releases cytokines that either interfere with viral replication or recruit more macrophages and immune cells at the site of activation.[11] Host innate immune signaling is mainly initiated by toll-like receptors (TLRs), RIG-I-like receptors (RLRs), and NOD-like receptors (NLRs) but other PRRs and free-molecule receptors also have minor contributions (1). Viral ssRNA is sensed by intracellular TLR7 receptor, which recruits a series of intracellular signaling molecules MyD88, IRAK-4, IRAK-1, TRAF6, and IRAF-7. IRAF7 upregulates the expression of Type 1 IFN. Collectively, intracellular PRRs attaching to PAMPs dictate the host's immune response to successfully abrogate infections of SARS-CoV-2 and prevent severe disease manifestations.[1]

1.1. Toll-like receptors

Toll-like receptors (TLRs) are extracellular PRRs found on the cell membrane and in endosomes and among the largest classes of PRRs. The transcription factors including NF-kB and mitogen-activated protein kinases (MAPKs) influence two signaling pathways: MyD88-dependent pathway, which activates immune-inflammatory factors, and the TRIF-dependent pathway that activates type I interferons and inflammatory factors.[1] Polymorphisms of TLRs, particularly TLR2 and TLR4, are risk genotypes for severe SARS-CoV infection.[12]

1.2. Retinoic-acid inducible Gene-I-like receptors

Retinoic acid-inducible gene I (RIG-I)-like receptors (RLRs) are cytosolic PRRs that contribute to the detection of RNA viruses to regulate inflammasome, type I and type III interferons and pro-inflammatory cytokines through downstream induction of interferon regulatory factor-3 (IRF-3), interferon regulatory factor-7 (IRF-7) and NF-kB.[13,14] During the SARS-CoV-1 epidemic, RLRs were reported to induce pro-inflammatory cytokines including IL-6, IL-8, and type I interferons in vitro through interferon-stimulation genes (ISGs).[15,16] While SARS-CoV has been associated with the release of ISGs, the mechanisms have not been understood for SARS-CoV-2 causality and ISG signaling responses.

1.3. Nucleotide-binding and oligomerization binding-like receptors

Nucleotide-binding and oligomerization domain (NOD)-like receptors (NLRs) are cytosolic PRRs that form multi-protein complexes known as inflammasomes and regulate the inflammatory signaling pathways of IFNα and IFNλ, thus regulating viral replication in bronchial epithelial cells.[15,17] It has been observed that modulation of NOD signaling pathways using human B-defensin 2 regulates and potentiates the induction of antigen-specific and virus-neutralizing antibodies in vivo in the receptor-binding domain (RBD) of MERS-CoV.[18]

Dysfunctional immune-pathogenesis

There is microvascular damage induced on the vasculature of human hosts in SARS-CoV-2 infection. In addition, there is underlying apoptosis that is the result of innate immune mechanisms, including pro-inflammatory cytokines. While viral antigens mediate this, the human hosts may develop an exaggerated response that leads to the further activation of cytokines and chemokines.[19] The clinical entity termed for a dysfunctional immune response is the cytokine storm syndrome (CSS). Various markers have been implicated in the development of the aberrant immune responses against SARS-CoV-2 infection. A robust overview of the relevant elevated markers in CSS is presented in Table 1.

Table 1: Trends of immune-clinical parameters of COVID patients on admission.

Marker	Key Findings	Reference
Serum ferritin, µg/L	Mean ferritin level 1418.3 µg/L in non-survivors vs 481.2 µg/L in survivors	[20]
	Mean ferritin level 1435.3 µg/L in non-survivors vs 503.2 µg/L in survivors	[21]
Erythrocyte sedimentation rate (ESR), mm/hr	Mean ESR level 38.5 mm/hr in non-survivors vs 28.0 mm/hr in survivors	[20]
Procalcitonin, ng/mL	Mean procalcitonin level 0.33 ng/mL in non-survivors vs 0.05 ng/mL in survivors	[20]
D-dimer, mg/L	Mean d-dimer level 4.6 mg/L in non-survivors vs 0.6 mg/L in survivors	[20]
	Mean d-dimer level 4.14 mg/L in ICU patients vs 1.66 mg/L in non-ICU patients	[22]
	Mean d-dimer level 5.2 mg/L in non-survivors vs 0.6 mg/L in survivors	[21]
	Mean d-dimer level 2.4 mg/L in ICU patients vs 0.5 mg/L non-ICU patients	[23]
	Mean d-dimer level 1.1 mg/L in non-survivors vs 0.5 mg/L in survivors	[24]
C-reactive protein (CRP), mg/L	Mean CRP level 113.0 mg/L in non-survivors vs 26.2 mg/L in survivors	[20]
	Mean CRP level 86.4 mg/L in non-survivors vs 36.0 mg/L in survivors	[24]
Lactate dehydrogenase (LDH), U/L	Mean LDH level 564.5 U/L in non-survivors vs 268.0 U/L in survivors	[20]
	Mean LDH level 435 U/L in ICU patients vs 212 U/L in non-ICU patients	[22]
	Mean LDH level 521 U/L in non-survivors vs 253.5 U/L in survivors	[21]
	Mean LDH level 400 U/L in ICU patients vs 281 U/L in non-ICU patients	[23]
Interleukin-2 receptor (IL-2R), U/L	Mean IL-2R level 1189 U/L in non-survivors vs 566.5 U/L in survivors	[20]
Interleukin-6 (IL-6), pg/mL	Mean IL-6 level 72.0 pg/mL in non-survivors vs 13.0 pg/mL in survivors	[20]
	Mean IL-6 level 11.0 pg/mL in non-survivors vs 6.3 pg/mL in survivors	[21]
Interleukin-10 (IL-10), pg/mL	Mean IL-10 level 12.8 pg/mL in non-survivors vs 5.0 pg/mL in survivors	[20]

The dysfunctional immune response is associated with widespread involvement and the development of respiratory failure in severely infected patients.[25] Inflammatory markers that are being monitored closely and serve as indicators of clinical severity include ferritin, CRP, ESR, and LDH. However, certain cytokines such as IL-2, IL-6, and IL-10 are also closely associated with severity.[20,24] These findings demonstrate the underlying inflammatory state of moderate-to-severe patients and identify the relevance of anti-inflammatory medications. It is important to note that only certain patients develop cytokine storm syndrome. While corticosteroids are not being routinely used in COVID-19, dexamethasone has reduced the mortality of COVID-19 by up to one-third in a recent trial.[26] Combining anti G-CSF antibodies with steroids has been observed to work synergistically and ought to be considered to improve the efficacy of therapeutic interventions and outcomes in COVID-19 patients.[27] Recent Interleukin-6 (IL-6) receptor blocker (tocilizumab) administered to patients who have elevated IL-6 levels is shown to reduce the risk of severe COVID-19 clinical phenotypes and mortality.[28] The monitoring of these markers is relevant as the identification of at-risk patients will determine necessary medical management. A thorough understanding of the underlying immune mechanisms provides the opportunity to adequately treat the infection in severe patients who may be at higher risk of mortality.

Relevance of Trained Innate Immunity during SARS-CoV-2 Infection

Innate immunity has multiple cell types that are associated with pathogen recognition and resistance against pathogens. Vaccinations such as BCG and endemic infections confer and trigger antimicrobial resistance, known as trained innate immunity. There has

been evidence of the durable memory of myeloid cells conferring trained immunity with their memory function. This function has gained recognition with the hypothesis that environmental contribution is paramount to developing innate immunity throughout life. Innate immunity is known to have originated through ontogeny. However, epigenetic reprogramming has also been observed with various responses against microbes such as activation, priming, and tolerance. So far, DNA methylation has been observed through epigenetic reprogramming to impact the myeloid cell function and trained immunity. There are multiple regulatory checks during the DNA methylation and genomic imprinting that may form the crux of the discussion of trained immunity related to myeloid cell adaptability. During the COVID-19 pandemic, BCG vaccination has found attraction given its ability to impact the innate immunity at the level of bone marrow progeny, specific to myeloid cells. The myeloid cells are part of the first line of defense and are relevant in trained immunity due to the ability of hematopoietic stem cells of myeloid origin to be primed. Similarly, an argument may be made in favor of pediatric SARS-CoV-2 infection and the vaccination programs received by children. As such, pediatric SARS-CoV-2 infection has been observed to be less severe than adult SARS-CoV-2 infection. While the angiotensin-converting enzyme-2 levels are lower in children than their adult counterparts, the relevance of trained innate immunity is considerable. Similarly, tuberculosis (TB) endemic regions have had a lower rate of COVID-19 mortality which may be explained by the underlying latent TB burden in these geographical pockets.

Immunotherapy Agents for SARS-CoV-2 Infection

Immunotherapy has been approved for the treatment of various cancers and viral infections. However, SARS-CoV-2 infection presents with severe inflammation and a dysfunctional immune response. The immunotherapy agents that have had some efficacy with SARS-CoV-2 infections include plasma therapy and cytokine-based immunotherapy. With plasma therapy, either convalescent serum or plasma of recovered patients is used that contains a high level of antibodies.[29] The specific antibodies in the recovered SARS-CoV-2 patients can neutralize the pathogen in the patients receiving plasma therapy. Plasma therapy has been used in previous epidemics of coronaviruses as well as the outbreak of Ebola virus in 2014 and H1N1 influenza pandemic in 1918.[30,32] In addition, plasma therapy was observed to show efficacy during severe SARS-CoV-2 infection with the absorption of lung lesions in the patients who received it.[33]

Cytokine storm syndrome as a characterizing feature of acute respiratory distress syndrome (ARDS) has been reported in SARS-CoV-2 infection with the elevation of proinflammatory chemokines and cytokines. Interferon (IFN) based immunotherapy has been noted to have some degree of efficacy during the severe phase of SARS-CoV-2 infection when the cytokine storm is present.[34] Evidence suggests that IFN-based immunotherapy can reduce viral replication and the response to treatment depends on the age of infected patients. IFN production is typically higher in adult patients and might effectively reduce the progression of SARS-CoV-2 infection.[34] IFN-based therapy includes IFN-α and -β with clinical trials that are being conducted for the efficacy of recombinant forms of IFN-based therapy in the early and late stages of SARS-CoV-2 infection.[35] IFN-λ has also gained some attraction for its potential as a candidate for SARS-CoV-2 infection management.[34] However, as of now, there is insufficient evidence to demonstrate the efficacy of IFN-based immunotherapy, especially in acute infection, and these therapies are being tested in clinical trial settings.[36]

CONCLUSION

Innate immunity during SARS-CoV-2 infection plays a critical role to determine the disease course and progression. The innate immune mechanisms by the host are often countered by viral evasion responses. Trained innate immunity is gaining prominence during the ongoing pandemic. BCG vaccination has been cited as a benchmark to determine the role of trained immunity in TB endemic regions. However, the overall impact of trained innate immunity is not clear. Thus, its relevance in the current and upcoming infectious disease outbreaks is considerable. Our findings demonstrate various aspects that contribute to the pathological host innate immune responses, inadvertently leading to dysfunctional adaptive immune responses. The immunotherapy agents have shown minimal efficacy with some benefit in more severe patients. With an effort to decipher the underlying mechanisms and longevity of trained immune responses across the globe, immunological responses to SARS-CoV-2 will help guide the management of morbidity and mortality due to severe infection. To conclude, the relevance of innate immunity is paramount, yet there are variances across the globe that need to be better elucidated.

DISCLOSURES

There is no conflict of interest and the authors did not receive any financial support for their work.

REFERENCES

1. Akira S, Uematsu S, Takeuchi O. Pathogen recognition and innate immunity. Cell, 2006; 124(4): 783–801.
2. Guo YR, Cao QD, Hong ZS, Tan YY, Chen SD, Jin HJ, et al. The origin, transmission and clinical therapies on coronavirus disease 2019 (COVID-19) outbreak- A n update on the status. Vol. 7, Military Medical Research. 2020.
3. Dhar SK, Vishnupriyan K, Damodar S, Gujar S, Das M. IL-6 and IL-10 as predictors of disease severity in COVID-19 patients: results from meta-analysis and regression. Heliyon, 2021; 7(2): e06155.
4. Netea MG, Quintin J, Van Der Meer JWM. Trained immunity: a memory for innate host defense. Cell

Host Microbe., 2011; 9(5): 355–61.
5. Netea MG, Giamarellos-Bourboulis EJ, Domínguez-Andrés J, Curtis N, van Crevel R, van de Veerdonk FL, et al. Trained Immunity: a Tool for Reducing Susceptibility to and the Severity of SARS-CoV-2 Infection. Vol. 181, Cell., 2020; 969–77.
6. Nankabirwa V, Tumwine JK, Mugaba PM, Tylleskär T, Sommerfelt H. Child survival and BCG vaccination: a community based prospective cohort study in Uganda. BMC Public Health, 2015; 15(1): 1–10.
7. Sarfraz Z, Sarfraz A, Pandav K, Makkar SS, Siddiqui SH, Patel G, et al. Variances in BCG Protection against COVID-19 Mortality: A Global Assessment. J Clin Tuberc Other Mycobact Dis., 2021;100249.
8. Moore RS, Kaletsky R, Murphy CT. Piwi/PRG-1 argonaute and TGF-β mediate transgenerational learned pathogenic avoidance. Cell, 2019; 177(7): 1827–41.
9. Berendsen M, Øland CB, Bles P, Jensen AKG, Kofoed PE, Whittle H, et al. Maternal priming: BCG-scarring in the mother enhances the survival of children with a BCG-scar. J Pediatr Infect Dis Soc., 2019; 10.
10. Hato T, Dagher PC. How the innate immune system senses trouble and causes trouble. Clin J Am Soc Nephrol., 2015; 10(8): 1459–69.
11. Duque GA, Descoteaux A. Macrophage cytokines: Involvement in immunity and infectious diseases. Vol. 5, Frontiers in Immunology, 2014.
12. Yuan FF, Boehm I, Chan PKS, Marks K, Tang JW, Hui DSC, et al. High prevalence of the CD14-159CC genotype in patients infected with severe acute respiratory syndrome-associated coronavirus. Clin Vaccine Immunol., 2007; 14(12): 1644–5.
13. Castanier C, Zemirli N, Portier A, Garcin D, Bidère N, Vazquez A, et al. MAVS ubiquitination by the E3 ligase TRIM25 and degradation by the proteasome is involved in type I interferon production after activation of the antiviral RIG-I-like receptors. BMC Biol., 2012; 10.
14. Odendall C, Dixit E, Stavru F, Bierne H, Franz KM, Durbin AF, et al. Diverse intracellular pathogens activate type III interferon expression from peroxisomes. Nat Immunol., 2014; 15(8): 717–26.
15. Yoshikawa T, Hill TE, Yoshikawa N, Popov VL, Galindo CL, Garner HR, et al. Dynamic innate immune responses of human bronchial epithelial cells to severe acute respiratory syndrome-associated coronavirus infection. PLoS One., 2010; 5(1).
16. Totura AL, Baric RS. SARS coronavirus pathogenesis: Host innate immune responses and viral antagonism of interferon. Vol. 2, Current Opinion in Virology, 2012; 264–75.
17. Hornung V, Ablasser A, Charrel-Dennis M, Bauernfeind F, Horvath G, Caffrey DR, et al. AIM2 recognizes cytosolic dsDNA and forms a caspase-1-activating inflammasome with ASC. Nature, 2009; 458(7237): 514–8.
18. Kim J, Yang YL, Jang SH, Jang YS. Human β-defensin 2 plays a regulatory role in innate antiviral immunity and is capable of potentiating the induction of antigen-specific immunity. Virol J., 2018; 15(1).
19. Yang M. Cell Pyroptosis, a Potential Pathogenic Mechanism of 2019-nCoV Infection. SSRN Electron J. 2020.
20. Chen T, Wu D, Chen H, Yan W, Yang D, Chen G, et al. Clinical characteristics of 113 deceased patients with coronavirus disease, 2019; Retrospective study. BMJ., 2020; 368.
21. 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(10229): 1054–62.
22. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical Characteristics of 138 Hospitalized Patients with 2019 Novel Coronavirus-Infected Pneumonia in Wuhan, China. JAMA - J Am Med Assoc., 2020; 323(11): 1061–9.
23. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet., 2020; 395(10223): 497–506.
24. Du RH, Liang LR, Yang CQ, Wang W, Cao TZ, Li M, et al. Predictors of mortality for patients with COVID-19 pneumonia caused by SARSCoV- 2: A prospective cohort study. Eur Respir J., 2020; 55(5).
25. Zhang B, Zhou X, Qiu Y, Feng F, Feng J, Jia Y, et al. Clinical characteristics of 82 death cases with COVID-19. medRxiv [Internet]., 2020 Jan 1; 2020.02.26.20028191. Available from: http://medrxiv.org/content/early/2020/02/27/2020.02.26.20028191.abstract
26. University of Oxford. Low-cost dexamethasone reduces death by up to one third in hospitalised patients with severe - The RECOVERY Trial. Oxford. 2020.
27. Banuelos J, Cao Y, Shin SC, Bochner BS, Avila P, Li S, et al. Granulocyte colony-stimulating factor blockade enables dexamethasone to inhibit lipopolysaccharide-induced murine lung neutrophils. PLoS One., 2017.
28. Guaraldi G, Meschiari M, Cozzi-Lepri A, Milic J, Tonelli R, Menozzi M, et al. Tocilizumab in patients with severe COVID-19: a retrospective cohort study. Lancet Rheumatol., 2020.
29. Sarfraz A, Singh-Makkar S, Sarfraz Z, Hathaway III PT. Therapeutic plasma exchange and COVID-19: a rapid review. J Clin Immunol Immunother., 2020; 6: 41.
30. Cherry JD, Krogstad P. Sars: The first pandemic of the 21 st century. Pediatr Res., 2004; 56(1): 1–5.
31. Roback JD, Guarner J. Convalescent plasma to treat COVID-19: possibilities and challenges. Jama., 2020; 323(16): 1561–2.
32. Chen L, Xiong J, Bao L, Shi Y. Convalescent

plasma as a potential therapy for COVID-19. Lancet Infect Dis., 2020; 20(4): 398–400.
33. Duan K, Liu B, Li C, Zhang H, Yu T, Qu J, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci., 2020; 117(17): 9490–6.
34. Mirtaleb MS, Mirtaleb AH, Nosrati H, Heshmatnia J, Falak R, Emameh RZ. Potential therapeutic agents to COVID-19: An update review on antiviral therapy, immunotherapy, and cell therapy. Biomed Pharmacother, 2021; 111518.
35. Korsukewitz C, Reddel SW, Bar-Or A, Wiendl H. Neurological immunotherapy in the era of COVID-19—looking for consensus in the literature. Nat Rev Neurol., 2020; 16(9): 493–505.
36. Esmaeilzadeh A, Elahi R. Immunobiology and immunotherapy of COVID-19: A clinically updated overview. J Cell Physiol., 2021; 236(4): 2519–43.