IJPSR (2020), Volume 11, Issue 11 (Review Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 03 May 2020; received in revised form, 12 October 2020; accepted, 19 October 2020; published 01 November 2020

TARGET BASED PHARMACOLOGICAL APPROACHES FOR DRUG DEVELOPMENT AGAINST NOVEL CORONA VIRUS (COVID-19)

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Keywords:

COVID-19, Hydroxychloroquine, Methylcobalamine, Valproic acid, BCG vaccine, Plasma therapy, ACE2 receptor, Vitamin D, Zinc

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ABSTRACT: The novel coronavirus (COVID-19) outbreak has covered almost 185 countries worldwide, causing infection to 32, 50,000 people and the death of approximately 2, 30,000 people to date. World Health Organisation (WHO) has declared it a pandemic that seems to be unstoppable as no vaccine or drug is available as of now to kill the virus. Several research labs are trying to develop a vaccine against the virus as soon as possible. Several drugs, like a combination of hydroxychloroquine and azithromycin, have been shown to be beneficial in COVID-19 infected patients. *In-silico* experiments suggest that methylcobalamin and valproic acid can reduce virus titer and thereby reducing the severity of the infection. BCG vaccine may provide immunity against the infection of coronavirus. As there is a strong correlation between the immune system of the infected person and the virulence of coronavirus, any therapy which could help in boosting the immune system shall be of prime importance. Hence, the efficacy of convalescent plasma therapy has been tried in COVID-19 infection, thinking that the antibodies from convalescent plasma might suppress viremia. Angiotensin-converting enzyme 2 (ACE2) receptors have been shown to be the entry point in human cells for COVID-19. RNA dependent RNA polymerase (RdRp) of the virus could be a potent target for inhibitor drug design and discovery against COVID-19. Recently, non-classical actions of vitamin D have been recognized. It affects upon cell proliferation and differentiation as well as immunologic functions resulting in an ability to maintain tolerance and to promote protective immunity. Zinc has been shown to affect multiple aspects of the immune system. Zinc has a significant role in the normal development and function of cells mediating innate immunity, neutrophils, and natural killer (NK) cells. The deficiency of zinc affects macrophages, phagocytosis, cytokine production, and intracellular killing. As there is a strong correlation between the immune system of the infected person and the virulence of coronavirus, any therapy which could help in boosting the immune system shall be of prime importance.

INTRODUCTION: Today, the whole human population is facing the threat of novel coronavirus (COVID-19) infection.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.11(11).5284-89

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.11(11).5284-89

The first case was reported in December 2019 from Wuhan city, Hubei province, China [1]. The pathogen was identified as SARS-CoV like a virus causing "pneumonia of unknown etiology" on January 8, 2020 [2].

Later, it was reported to be transmitted from human-to-human. Till now, the virus has spread to 185 countries infecting 35 million peoples. World Health Organization (WHO) has declared it a pandemic.

To date more than 1 million people have died due to a severe respiratory problem caused by a novel coronavirus (COVID-19). The infection spreading rate can be understood by the reproductive number (R0) value of this virus 3. R0 value of COVID-19 ranges from 2-5, which means an infected person can infect 2-5 persons either by coming into contact with them or by spreading viral particles by sneezing and coughing around them. The R0 values have important implications for predicting the effects of pharmaceutical and nonpharmaceutical interventions. Few methods of nonpharmaceutical interventions are social distancing, contact tracing, and quarantine [3].

In view of the current outbreak and death toll scenario, novel drug design and discovery is a challenge constrained by time. On the other hand, drug repurposing and trial of available therapy as prophylactic as well as treatment, could help in the prevention and management of the coronavirus infection.

According to the virologists, coronaviruses are a large family of viruses that belongs to the Coronaviridae family. These viruses have the largest RNA genome of 26-32 kilobases (kb) with a positive-sense single strand [4]. The viral genome encodes four different structural proteins. These are nucleocapsid (N), spike (S), membrane (M), and envelope (E) [5]. Spike (S) and membrane (M) is a glycoprotein, while envelope (E) is the non-glycosylated protein [6]. The viral envelope interacts with the host cell membrane to initiate the infection. Spike protein is important for receptor binding, membrane fusion, internalization of the virus, tissue tropism, and host range. Due to this fact S protein is an important target for vaccine development [7].

The gene for viral spike (S) glycoprotein has a greater frequency of recombination in the coronaviruses. Novel coronaviruses such as Covid-19 has emerged due to RNA recombination without a proof-reading mechanism amongst the existing coronaviruses. Some members of this family, such as Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV-1), and Middle East Respiratory Syndrome Corona Virus (MERS-CoV) have been found to infect animals as well as humans. The novel coronavirus (Covid-19), which has become pandemic, causes severe acute respiratory syndrome in humans only. That is why this virus is also called as SARS-CoV-2. The length of the Covid-19 encoded proteins was found to be almost similar to bat SARS-like coronaviruses. However, a notable difference was found in the longer spike protein of Covid-19 when compared with the bat SARS-like coronaviruses and SARS-CoV-2 [8].

Signs and Symptoms of Infection Caused by Covid-19: Patients are mainly reported with pneumonia-like symptoms, high-grade fever, shortness of breath (dyspnoea), dry cough, headache, and fatigue. Blood estimations will show lymphopenia, an elevated level of lactate dehydrogenase, and prolonged prothrombin time. Chest radiographs show patchy bilateral shadows or ground glass, including invasive pneumonic infiltrates [9, 10]. As the disease progresses, it may result in respiratory failure owing to alveolar damage and even death. There are several pharmacological challenges in controlling the infection because the severity of infection caused by the virus depends on the host immune system, health condition, and disease history of the patient.

Current Researches Suggesting a Potential Target for the Development of Drugs or Vaccines against Covid-19 Infection: A. Angiotensin-Converting Enzyme 2 (ACE2) is present on the cell membranes where the SARS-CoV binds and gets entry inside the cell. The human version of the enzyme is often referred to as hACE2 [11]. Studies on virus infection suggest that 2019-nCoV is able to use the ACE2 proteins as an entry receptor to enter ACE2-expressing cells indicating that ACE2 is probably the cell receptor through which COVID-19 virus enters the human cells. A recent study based on structural analysis of the virus particles suggests SARS-CoV-2 has a higher affinity to the receptor needed for cell entry providing a molecular basis for the high infectiousness of SARS-CoV-2 [12]. It has also been found that 2019-nCoV does not use other coronavirus receptors, such as aminopeptidase N (APN) and dipeptidyl peptidase 4 (DPP4) [13].

B. Attachment inhibitors designed for SARS-CoV: The S-glycoprotein of COVID-19 is a vital part of the virus envelope through which the virus gets attached to the host cell receptor.

COVID-19 virus interacts with the host receptor using novel glycosylation sites, thereby affecting the internalization process and its associated pathogenesis [7]. The COVID-19 has few antigenic similarities with SARS coronavirus, which is associated with a similar antigenic response. Therefore, this similarity has been considered as one of the preventive strategies based on S-glycoprotein peptide-based vaccine designed for SARS-CoV.

C. RNA-dependent RNA Polymerase Inhibitors (nsp12 Protein Inhibitor): There is an urgent need for the identification of new molecules that can reduce viral titers and thus limit the severity of the disease. A gene at the 5' end known as ORF1AB is found in the genome of COVID-19 that encodes for all the polyprotein of the non-structural proteins 14. This polyprotein undergoes proteolytic processing and gives rise to sixteen different proteins, namely non-structural proteins nsPs 1-16 [15]. The protein nsP3 has an adenosine diphosphate-ribose 1"-phosphatase activity [16,] while the protease activity responsible for the cleavage of the polyprotein is present in the nsP5 protein. The nsP12 protein houses the RNA-dependent RNA polymerases and is responsible for duplication of the genome. The nsP13 protein has RNA helicase activity that is critical for genome duplication. The nsP14 protein has exoribonuclease (exoN) and N7-methyltransferase activities [17]. The nsP15 protein contains a Nidoviral ribonuclease specific for U, while the nsP16 protein has a SAM-dependent O-methyl-transferase activity [14].

Structure of the SARS nsp12 (6NUR) was used as a reference model to prepare a homology model of nsP12 for COVID-19. The model can be used to carry out in silico screening for the identification of molecules of natural products or FDA approved drugs to inhibit the activity of nsP12. Vitamin B12 (methylcobalamin) was shown to bind to the active site of the nsP12 protein [18]. *In-silico* model of the nsp12 in complex with substrate RNA and incoming nucleoside triphosphate (NTP) showed that Vitamin B12 binding site overlaps with that of the incoming nucleotide. It is, therefore, possible that Vitamin B12 (methylcobalamin) binding may prevent association with RNA and NTP and thus inhibit the RNA-dependant RNA polymerase (RdRP) activity of nsp12.

Hence, it can be suggested that methylcobalamin form of vitamin B12 may serve as an effective inhibitor of the nsp12 protein of COVID-19 [18]. Similarly, Valproic acid has also been studied, and *in-silico* results indicate that valproic acid may also be the possible inhibitors of the RNA-dependent-RNA polymerase (RdRP) activity of the nsP12 enzyme of COVID-19 [19]. Since nsP12 is vital for the replication of the viral enzyme, its inhibition can decrease viral titers and reduce the severity of the COVID-19 disease. Hence, the ability of methylcobalamin and valproic acid to inhibit viral replication should be tested urgently using in vitro and in vivo experimental models.

D. Convalescent Plasma Therapy: Convalescent plasma therapy has been a successful trial done in hospitals of Delhi government in which plasma of recovered corona positive patients are being used. This process has been used in China and other countries with successful results in COVID-19 infected patients. The antibodies against the virus developed in COVID-19 infected and successfully recovered patients are transferred into the blood of newly infected patients through the plasma isolation technique.

The plasma contains the antibodies and prevents the virus from spreading. Convalescent plasma or immunoglobulins have been used as a last resort to improve the survival rate of patients with SARS whose condition continued to deteriorate despite treatment with pulsed methylprednisolone. Moreover, several studies showed a shorter hospital stay and lower mortality in patients treated with convalescent plasma than those who were not treated with convalescent plasma [20-22].

E. Clinical Trial for the Preventive Effect of BCG Vaccine against Coronavirus Infection: It has been noted that the incidence of COVID-19 in nations with a BCG vaccination protocol was 38.4 per million, while that in nations without BCG vaccination protocol was 358.4 per million.

The death rate in nations with a BCG vaccination program was found to be 4.28 per million, while in countries without the program, it was 40 per million. The data clearly shows that the difference in infection surges, and the death rate is almost 10 times.

The US and other countries without universal policies of BCG vaccination, like Italy and the Netherlands, have been more severely affected compared to countries with universal and long-standing BCG policies. Unlike other vaccines, the BCG vaccine may also boost the innate immune system, first-line defenses that keep more than one pathogens from causing an infection. According to the researchers, the vaccine is also believed to protect the body against different types of respiratory infections, which have similar symptoms to COVID-19. BCG vaccination protects against experimental viral infection in humans through the induction of cytokines associated with trained immunity [23].

A clinical trial with the title "BCG Vaccination to Reduce the Impact of COVID-19 in Australian Healthcare workers following Coronavirus exposure" has been started since March 30, 2020. An estimated 4170 participants shall be included in an interventional clinical trial and will be randomized to receive a single dose of BCG vaccine or no BCG vaccine. This is a phase III multicentric, open-label randomized controlled study that is expected to be completed by March 30, 2022. Participants will be followed-up for 12 months with regular mobile phone text messages (up to weekly) and surveys to identify and detail COVID-19 infection. Additional information on severe disease will be obtained from hospital medical records and government databases. Blood samples will be collected prior to randomization and at 12 months to determine exposure to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Where required, swab/blood samples will be taken at illness episodes to assess SARS-CoV-2 infection.

F. Clinical Trial for Prevention and Control of COVID-19 Infection using Hydroxychloroquine-Azithromycin (HCQ-AZ) Combination 24: A cohort of 1061 COVID-19 patients, treated for at least 3 days with the Hydroxychloroquine-Azithromycin (HCQ-AZ) combination and a follow-up of at least 9 days were investigated. A good clinical outcome and the virological cure was obtained in 973 patients within 10 days (91.7%). A poor outcome was observed for 46 patients (4.3%); 10 were transferred to intensive care units, 5 patients died (0.47%) (74-95 years old), and 31 required 10 days of hospitalization or more. Poor clinical outcome was significantly associated with older age, initial higher severity, and low hydroxyl-chloroquine serum concentration. In addition, both poor clinical and virological outcomes were associated with the use of selective beta-blocking agents and angiotensin II receptor blockers. Mortality was significantly lower in patients who had received > 3 days of HCQ-AZ than in patients treated with other regimens.

It was concluded that the HCQ-AZ combination, when started immediately after diagnosis, is a safe and efficient treatment for COVID-19, with a mortality rate of 0.5%, in elderly patients. It avoids worsening and clears virus persistence and contagiously in most cases. No cardiac toxicity was observed [24].

G. Optimum Vitamin D Level for Protective Immunity against Novel Coronavirus Infection: Vitamin D has been used (unknowingly) to treat infections such as tuberculosis before the advent of effective antibiotics. Cod liver oil, a rich source of vitamin D has also been employed as a treatment for tuberculosis as well as for generally increased protection from infections [25]. Individuals with lower vitamin D levels (<30 ng/ml) were more likely to self-report a recent upper respiratory tract infection than those with sufficient levels, even after adjusting for variables including season, age, gender, body mass, and race [26]. There have been a number of other cross-sectional studies looking at vitamin D levels and rates of influenza [27] and HIV [28, 29]. Calcitriol (1,25-dihydroxyvitamin D3) exerts a significant impact on ACE2 [30]. Lower vitamin D levels have been associated with increased rates of infection. A recent prospective, double-blind placebo study using nasopharyngeal swab culture (and not self-report), and a therapeutic dose of vitamin D showed that administration of vitamin D resulted in a statistically significant (42%) decrease in the incidence of influenza infection [31].

The effects on the innate immune system are responsible for the beneficial effects of vitamin D on protective immunity. Vitamin D inhibits B cell proliferation and blocks B cell differentiation and secretion of immunoglobulin [32, 33]. Vitamin D also suppresses T cell proliferation [34] and results in a shift from T helper cells 1 (Th1) to T helper cells 2

(Th2) phenotype [35, 36]. Furthermore, maturation of T cells is also affected, which makes them shiting away from the inflammatory Th17 phenotype [37, 38,] causing induction of T regulatory cells [39-42]. These effects result in increased production of anti-inflammatory cytokines such as IL-10 with decreased production of inflammatory cytokines (IL-17, IL-21). Vitamin D also inhibits monocyte production of inflammatory cytokines such as IL-1, IL-6, IL-8, IL-12, and TNFα [43]. H. Multiple targets for zinc and its role in COVID-19 protection: Zinc deficiency has been found to be responsible for 16% of all deep respiratory infections world-wide 44 providing a link of zinc deficiency with the risk and severe progression of COVID-19 infection. Zinc causes mucociliary clearance of virus 45 and has been shown to improve the integrity of lungs in a murine model of acute lung injury [46].

ACE-2 is a zinc-metalloenzyme and present on type 2 pneumocytes. Virus entry could be affected by alterations in zinc-dependent gene expression by these pneumocytes. Zinc may prevent the fusion of virus with the host membrane and decreases the viral polymerase function. Such activity results in impairing protein translation and processing, blocking viral particle release, and destabilize the viral envelope [47-49].

CONCLUSION: In this review article, it has been concluded that with a complete understanding of microbiology as well as pathogenicity, it has become possible to develop a drug with greater specificity. In order to develop a drug or injectable vaccine, the virus receptor can be targeted. Replication of the viral genome is an easy target that can be checked to control the virus propagation in the human cell. The human body's immune system can be a potential factor through which viruses can be defeated. Convalescent plasma therapy is a successful idea in this regard. At present, the virus is engulfing a large chunk of the world population, and scientists are in great need of effective therapy as soon as possible. Several pharmaceutical and clinical research organizations are trying to develop a drug. The fast track approval process would be an advantage in this fight against COVID-19 to save lives. In addition, given the urgency of the situation and the fact that methylcobalamin is already part of drug formulations, doctors may consider adding or increasing the dosage of methylcobalamin in their current patient care protocols since it can rapidly reduce the severity of the COVID-19 disease.

ACKNOWLEDGEMENT: Nil

CONFLICTS OF INTEREST: The authors have no conflict of interest to mention.

REFERENCES:

1. Li Q, Guan X, Wu P, Wang X, Zhou L and Tong Y: Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. New England Journal of Medicine 2020; 382: 1199-07.
2. WHO. Pneumonia of unknown cause—China. 2020, Jan 30.
3. Riou J and Althaus CL: Pattern of early human-to-human transmission of Wuhan 2019 novel coronavirus (2019-nCoV), December 2019 to January 2020. Eurosurveillance 2020; 25: 25.
4. Modrow S, Falke D, Truyen U, Schätzl H and Modrow S: Viruses with Single-Stranded, Positive-Sense RNA Genomes. Molecular Virology 2013; 185-49.
5. Shang W, Yang Y, Rao Y and Rao X: The outbreak of SARS-CoV-2 pneumonia calls for viral vaccines. NPJ Vaccines 2020; 5:18.
6. Ujike M and Taguchi F: Incorporation of spike and membrane glycoproteins into coronavirus virions. Viruses 2015; 7(4): 1700-25.
7. Alexandra WC, Joun PY, Alejandra TM, Abigail W and David V: Structure, function and antigenicity of the SARS-CoV-2 spike glycoprotein. Cell 2020; 180: 281-92.
8. Lu R, Zhao X, Li J, Niu P, Yang B and Wu H: Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. Lancet 2020; 395(10224): 565-74.
9. Huang C, Wang Y, Li X, Ren L, Zhao J and Hu Y: Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395(10223): 497-06
10. Wang D, Hu B, Hu C, Zhu F, Liu X and Zhang J: Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020; 323(11): 1061-69.
11. Kasmi Y, Khataby K and Souiri A: Coronaviridae: 100,000 years of emergence and reemergence. Elsevier 2019; 1: 135.
12. Wrapp D, Wang N, Corbett KS, Goldsmith JA, Hsieh CL and Abiona O: Cryo-EM structure of the 2019-nCoV spike in the prefusion conformation. Science 2020; 367: 1260-3.
13. Letko M, Marzi A and Munster V: Functional assessment of cell entry and receptor usage for SARS-CoV-2 and other lineage B betacoronaviruses. Natural Microbiology 2020; 5: 562-69.
14. Wu F, Zhao S, Yu B, Chen YM and Wang W: A new coronavirus associated with human respiratory disease in China. Nature 2020; 579: 265-69.
15. Graham, R.L, Sparks JS, Eckerle LD and Sims AC: Denison MR. SARS coronavirus replicase proteins in pathogenesis. Virus Research 2008; 133: 88-00.
16. Saikatendu KS, Joseph JS, Subramanian V, Clayton T and Griffith M: Structural basis of severe acute respiratory syndrome coronavirus ADPribose-1″-phosphate dephos-phorylation by a conserved domain of nsP3. Structure 2005; 13: 1665-75.

17. Emsley P and Cowtan K: Coot: model-building tools for molecular graphics. Acta Crystallogr D Biology Crystallography 2004; 60: 2126-32.
18. Narayanan N and Nair DT: Vitamin B12 may inhibit RNA-dependent-RNA polymerase activity of nsp12 from the SARS-C0V-2 Virus. Preprints 2020; 72(10): 2057-32.
19. Bhavesh NS and Patra A: Virtual screening and molecular dynamics simulation suggest valproic acid CO-A could bind to SARS-CoV2 RNA depended RNA polymerase. Preprints 2020; 03(01): 93.
20. Lai ST: Treatment of severe acute respiratory syndrome. European Journal of Clinical Microbiology of Infectious Disease 2005; 24: 583-91.
21. Soo YO, Cheng Y and Wong R: Retrospective comparison of convalescent plasma with continuing high-dose methylprednisolone treatment in SARS patients. Clinical Microbiology of Infection 2004; 10: 676-78.
22. Cheng Y, Wong R and Soo YO: Use of convalescent plasma therapy in SARS patients in Hong Kong. European J of Clinical Microbio of Infectious Dis 2005; 24: 44-46.
23. Arts RJW, Moorlag SJCFM and Novakovic B: BCG Vaccination Protects against Experimental Viral Infection in Humans through the Induction of Cytokines Associated with Trained Immunity. Cell Host Microbe 2018; 23(1): 89-100.
24. Gautret P, Lagier JC, Parola P and Raoult D: Hydroxy-chloroquine and azithromycin as a treatment of COVID-19: results of an open-label non-randomized clinical trial. Int J of Antimicrobial agents 2020; 56(01): 105949.
25. Williams C: On the use and administration of cod-liver oil in pulmonary consumption. London Journal of Medicine 1849; 1: 1-18.
26. Ginde AA, Mansbach JM and Camargo CA Jr:Association between serum 25-hydroxyvitamin D level and upper respiratory tract infection in the Third National Health and Nutrition Examination Survey. Arch Intern Med 2009; 169(4): 384-90.
27. Cannell JJ: Epidemic influenza and vitamin D. Epidemiology and Infection. 2006; 134(6): 1129-40.
28. Villamor E: A potential role for vitamin D on HIV infection. Nutrition Reviews 2006; 64: 226-33.
29. Rodriguez M: High frequency of vitamin D deficiency in ambulatory HIV-Positive patients. AIDS Research and Human Retroviruses 2009; 25(1): 9-14.
30. Cui C, Xu P and Li G: Vitamin D receptor activation regulates microglia polarization and oxidative stress in spontaneously hypertensive rats and angiotensin II-exposed microglial cells: Role of rennin-angiotensin system. Redox Biology 2019; 26.
31. Urashima M: Randomized trial of vitamin D supplementation to prevent seasonal influenza A in school children. The Am J of Clinical Nut 2010; 91(5): 1255-60.
32. Lemire JM: 1 alpha,25-dihydroxyvitamin D3 suppresses proliferation and immunoglobulin production by normal human peripheral blood mononuclear cells. Journal of Clinical Investigation 1984; 74(2): 657-61.
33. Chen S: Modulatory effects of 1,25-dihydroxyvitamin D3 on human B cell differentiation. Journal of Immunology 2007; 179(3): 1634-47.
34. Bhalla AK: 1,25-Dihydroxyvitamin D3 inhibits antigen-induced T cell activation. Journal of Immunology 1984; 133(4): 1748–54.
35. Mattner F: Inhibition of Th1 development and treatment of chronic-relapsing experimental allergic encephalomyelitis by a non-hypercalcemic analogue of 1,25-dihydroxy-vitamin D(3). Euro of Immunology 2000; 30(2): 498-08.
36. Boonstra A: 1alpha,25-Dihydroxyvitamin d3 has a direct effect on naive CD4(+) T cells to enhance the development of Th2 cells. J of Immunology 2001; 167(9): 4974-80.
37. Tang J:Calcitriol suppresses antiretinal autoimmunity through inhibitory effects on the Th17 effector response. Journal of Immunology 2009; 182(8): 4624-32.
38. Daniel C: Immune modulatory treatment of trinitrobenzene sulfonic acid colitis with calcitriol is associated with a change of a T helper (Th) 1/Th17 to a Th2 and regulatory T cell profile. Journal of Pharmacology and Experimental Therapeutics 2008; 324(1): 23-33.
39. Gregori S: Regulatory T cells induced by 1 alpha,25-dihydroxyvitamin D3 and mycophenolate mofetil treatment mediate transplantation tolerance. Journal of Immunology 2001; 167(4): 1945-53.
40. Barrat FJ: *In-vitro* generation of interleukin 10-producing regulatory CD4(+) T cells is induced by immune-suppressive drugs and inhibited by T helper type 1 (Th1)- and Th2-inducing cytokines. Journal of Experimental Medicine 2002; 195(5): 603-16.
41. Gorman S: Topically applied 1,25-dihydroxyvitamin D3 enhances the suppressive activity of CD4+CD25+ cells in the draining lymph nodes. Journal of Immunology 2007; 179(9): 6273-83.
42. Penna G: Expression of the inhibitory receptor ILT3 on dendritic cells is dispensable for induction of CD4+Foxp3+ regulatory T cells by 1,25-dihydroxyvitamin D3. Blood 2005; 106(10): 3490-7.
43. Almerighi C: 1Alpha, 25-dihydroxyvitamin D3 inhibits CD40L-induced pro-inflammatory and immune-modulatory activity in human monocytes. Cytokine 2009; 45(3): 190–7.
44. World Health Organization: The World Health report 2002. Midwifery 2003; 19:72–3.
45. Woodworth BA, Zhang S, Tamashiro E, Bhargave G, Palmer JN and Cohen NA: Zinc increases ciliary beat frequency in a calcium-dependent manner. American Journal of Rhinology and Allergy 2010; 24: 6–10.
46. Wessels I, Pupke JT, Trotha K-T von, Gombert A, Himmelsbach A and Fischer HJ: Zinc supplementation ameliorates lung injury by reducing neutrophil recruitment and activity. Thorax 2020; 75: 253-61.
47. Patel VB, Zhong J-C, Grant MB and Oudit GY: Role of the ACE2/Angiotensin 1-7 axis of the renin-angiotensin system in heart failure. Circu Res 2016; 118: 1313-26.
48. Suara RO and Crowe JE: Effect of zinc salts on respiratory syncytial virus replication. Antimicrobial Agents Chemotherapy 2004; 48: 783-90.
49. Kümel G, Schrader S, Zentgraf H, Daus H and Brendel M: The mechanism of the antiherpetic activity of zinc sulphate. Journal of General Virology 1990; 71: 2989-97.

How to cite this article:
Hoda Q, Fatma A, Pahwa S and C Gupta: Target based pharmacological approaches for drug development against novel corona virus (COVID-19). Int J Pharm Sci & Res 2020; 11(11): 5284-89. doi: 10.13040/IJPSR.0975-8232.11(11).5284-89.