IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 19, Issue 5 Ser.8 (May. 2020), PP 35-40
www.iosrjournals.org

Receptors Expression andTreatment Modalities of Corona Virus Disease 2019

Shravani Komuravelly[1], Ashwini Sherla[1], C.S Mujeebuddin[2]
1.Interns, Clinosol Research Pvt Ltd, Ameerpet, Hyderabad-500038, India.
2.C.E.O and Founder, Clinosol Research Pvt Ltd, Ameerpet, Hyderabad-500038, India

Abstract
The mutated human corona virus (SARS-CoV-2) of 2019 which was global pandemic is responsible for more than two lakh deaths as of now. The outbreak of SARS-CoV & MERS-CoV in 2002 and 2013 respectively are more lethal and has less ability to spread whereas SARS-CoV-2 is less lethal and has more ability to spread. There are certain differences& similarities in the genomic composition, incubation period and mechanism to cause infection among SARS-CoV and SARS-Co-V-2. Although COVID-19 cases are growing at a faster rate,the transmission rate in India is lower than in other countries. This was achieved by mandated lockdown at federal level to enforce physical distancing as well as mass testing which lead the curve to flatten and are also the key components to decrease the rate of infection and its ability to spread. Even though the Food and drug administration (FDA) approved emergency use drug Remdesivir is available. The disease is also being treated with anti-malarial, other anti-virals, anti-inflammatory and immunomodulators because there is a dearth of vaccine. In this text, a collective information on mechanism, pathogenesis, therapeutic targets, and recommendations of current clinical guidelines are provided.
Key words:*SARS-CoV-2, Global pandemic, COVID-19, Remdesivir, Vaccine.*

Date of Submission: 04-05-2020 Date of Acceptance: 18-05-2020

I. Introduction

Corona virus outbreak which was discoveredin December 2019 atWuhan; Hubei province of China is responsible for global pandemic caused bypathogenic severe acute respiratory syndrome coronavirus 2(SARS-CoV-2) [1]. Since the 2019 novel corona virus (2019-nCoV)is analogoustozoonotic severe acute respiratory syndrome - related coronavirus(SARS CoV) with ~76% amino acid identitywhich was the cause for epidemicsevereacute respiratory syndrome (SARS) in 2002[2,3]. The international committee on taxonomy of virus (ICTV) classified 2019-nCoV as SARS-CoV-2[4].On Jan 30 2020, after the report of disease, the world health organization(WHO) declared SARS-CoV-2 as a public health emergency of international concern (PHEIC)[5] and on Feb 11 2020, WHO named tentative2019-nCoV as Corona virus disease 2019 (COVID-19)[6] and on March 11 2020,it declared COVID-19 as global pandemic because of its substantialspread across the world[7].

In COVID-19, the virus circulating among bats which are a natural reservoir startedmutating and infecting an intermediate host pangolin [8]. In late 2019, disease outbreak in humans began in China but has spread around the world. As of May 042020, there have been 35,57,235laboratory confirmed cases of COVID-19 and 2,45,150deaths resulting the fatality rate of 3.4%. This serves the average across more than 200countries[9]. It is worth pointing that fatality rates for elderly (>60yrs) are high and they are the ones at highest risk. Similarly, the fatality rate is higher among folks with comorbidities such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, obesity,malignancy and immunocompromised[10,11].Regardlessof age and comorbidities the other risk factor is gender, a recent study showed that men are 2.5 times more prone to the disease than women[12].

Based on the current data over 80% of patients with COVID-19 have mild infection and some people do not develop the symptoms at all, the remaining proportion develop symptoms such as fever, head ache, shortness of breath(SOB),sore throat, cough, fatigue, myalgia, loss of smell (anosmia)and taste(ageusia), some rarely occurring are diarrhea,conjunctivitis (pink eye), skin rash, inflammation of toes (COVID toes) and all the way to serious problems like interstitial pneumonia. Acute respiratory distress syndrome (ARDS) and septic shock are the main complications of death for people with infection [13-16]. These symptoms may occur after an average of 14 days of incubation period after transmission of virus [17].

In addition of causing disease the virus spreads quickly usually through respiratory droplets, aerosolsand contact routes (direct contact with infected person and indirect contact with surfaces or objects used on/by infected person)and this aids in air borne, local andcommunitytransmissions[18]. Indian researchers claim

that corona viruses exist in 11 strains, the most dominant A2a form is verge on spread[19]. Viruses are given reproductive number/R_0 based on how quickly they spread. The current estimate of COVID-19 is R_0~2.5[20].

RECEPTOR EXPRESSION AND PATHOGENESIS

The ICTV based hierarchical classification of coronaviruses denotes the order, family as Nidovirales and Coronaviridae respectively and it states that the genera of viruses which are 4 in number as α,β,γ and δ. The genus to which SARS-CoV-2 belongs is β genus. The viral genome containing positive-sense single stranded ribose nucleic acid(ssRNA)also encrypts 4 structural proteins and are spike protein (S), envelop protein(E), nucleocapsid protein(N) and membrane protein(M) (Figure 1). The S-glycoprotein present on itssurface combines with the host cellular receptors to trigger the infection [21]. The N-terminal domain insertion of s-protein also confabulate with sialic acid binding action [22].It also contains non-structural proteins such as RNA-dependent RNA polymerase(RdRp),Coronavirus main protease(3CLpro),papain-like-protease(PLpro)[23,24].

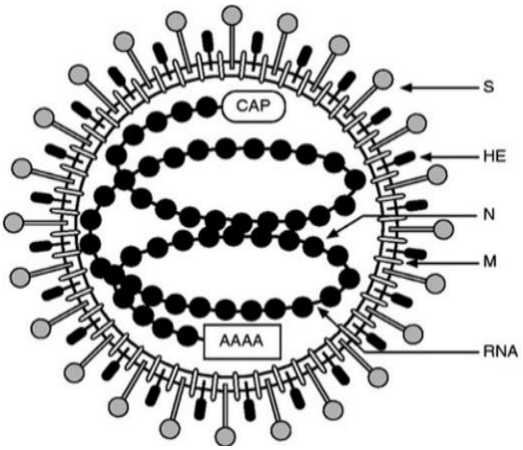

Figure 1: SARS-CoV-2

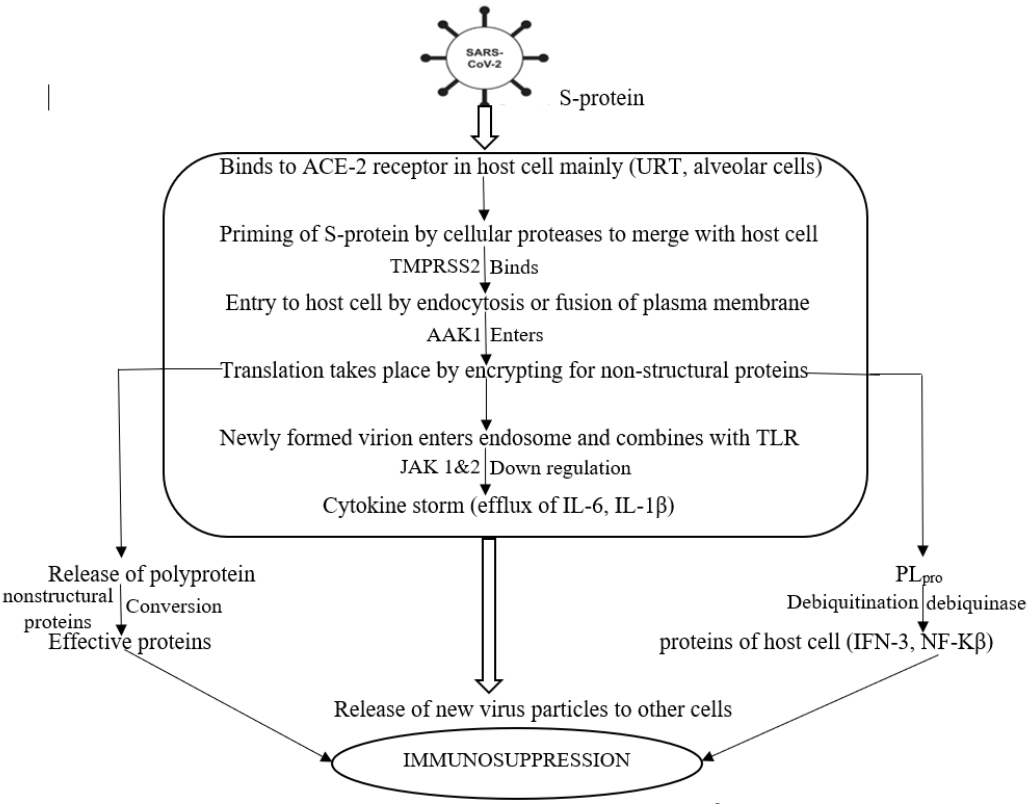

Figure 2: Pathogenesis of SARS-CoV-2©

NOTE: ACE-2- angiotensin converting enzyme-2, URT-upper respiratory tract, TMPRSS2- transmembrane serine protease -2, AAK1-AP2-associated protein kinase 1 TLR- toll-like receptors, JAK- Janus kinases, IL-6-interleukin-6, IL-1β-interleukin 1β, IFN-3-interferon-3, NF-Kβ- nuclear factor kappa light chain enhancer of beta cells.

TESTINGAND LABORATORY FINDINGS

The real-time reverse transcription polymerase chain reaction (rRT-PCR) testused in COVID-19 is only for use under the Food and Drug Administration's Emergency Use Authorisation (FDAEUA)for the detection of nucleic acid from upper and lower respiratory specimens (such as nasal, nasopharyngeal or oropharyngeal swabs, sputum, lower respiratory tract aspirates and bronchoalveolar lavage).Results for the identification of SARS-CoV-2 RNA is generally detectable during the acute phase of infection. Positive results are indicative of the presence of SARS-CoV-2 RNA.But positive results may not exclude bacterial infection or co-infection with other viruses and negative results do not preclude SARS-CoV-2 infection. So, the test should not be the lone basis for patient management decisions. Collaborative chest computed tomography (CT) which is more accurate in testing SARS-CoV-2 and loop mediated isothermal amplification (LAMP) are also applied to detect COVID-19[25-27].

Nasopharyngeal swab which was quite risky in obtaining the samplegained an advantageous, quicker, reliable alternative,Saliva testing approved for use underFDAEUA [28].

Pulse oximeter is a device clip onto patients finger for reading of oxygen level in blood. The SOB being a main symptom of COVID-19 the device is in use as the early caution to know the oxygen saturation levels (below 95%). But some factors such as nail polish, artificial nails, cold hands and poor circulation interferes with the device accuracy[29].

The researchers developed a low-cost respiratory swab test that can diagnose COVID-19 infection in about 45 minutes.SARS-CoV-2 DETECTR a clustered regularly interspaced short palindromic repeats (CRISPR) based gene targeting technology that is unique to SARS-CoV-2.The test provides easy interpretationin the presence of SARS-CoV-2 genes. The U.S. Food and Drug Administration (USFDA) haveyet to approve the test [30].

Leukopenia, leucocytosis, lymphopenia, thrombocytopeniaand neutrophilia areseen. ProcalcitoninLactate dehydrogenase, ferritin levels, c-reactive protein, serum IL-6 and D-dimer levels are elevated [31-32].

TREATMENT

As of now, there are no FDA approved drugs for treating of SARS-CoV-2 infection so, the treatment is based on the type and phase of illness. In case of mild infection without symptoms the Centre for disease control (CDC) recommends self-quarantine for a weekthen discontinue the isolation if remains asymptomatic.If the individual's symptom prognosis gets worsen then get managed through ambulatory setting or get telemedicine contacting the health care professional. In case, the symptoms are irreversible get clinical assessment for oxygen saturation if SpO_2>93% then supportive care, administration of oxygen therapy and empiric antimicrobials are recommended. Critically ill patients requiresupportive care, fluids, supplemental oxygen, ventilatory and hemodynamic support[33].

The potential therapeutic strategies could possibly involve many mechanisms such like use of molecular strategy for repurposing of drugs that may have therapeutic effect on coronavirus or production of drug targets based on genomic information, receptor and amino acid binding, cellular protease activity, translation process, cytokine storm, structural and non-structural proteins which are responsible for its pathogenicity and viability.

Table 1: Therapeutic target considerations and their possible mechanisms [34]:

DRUG	TARGET	MECHANISM
Chloroquine and Hydroxychloroquine	ACE-2 receptors, viral sialic acid, endosome carrying SARS-Co-V-2.	Inhibits glycosylation of ACE-2 receptor thereby forbids the viral entry. Decreases the synthesis of viral sialic acid and suppresses the insertion of spike protein. Blocks the transport of SARS-Co-V-2 to endosomes resulting in inhibition of cytokine storm.
Umifenovir	S-protein/ACE-2 interaction	Inhibits membrane fusion of viral envelop
Lopinavir/ritonavir	3CLpro	Inhibits the 3CLpro protein, aftereffect suppresses the viral translation.
Remdesivir	Adenosine analogue, RdRp	This prodrug undergoes hydrolysis into active form and inhibit viral replication and RdRp.
Favipavir	RdRp	Inhibits the RdRp and forbids the viral replication.
Ribavirin	RdRp	Inhibits the RdRp and forbids the viral replication
Tocilizumab	Interleukin-6(IL-6) receptor	Inhibition of IL-6 receptor thereby restrains the cytokine storm leading to upregulation of

		inflammatory process.
Sarilumab	IL-6 receptor	Inhibits the IL-6 receptor and hinders the cytokine storm.
Baricitinib	Janus kinase 1&2(JAK1&2), AAK1	Inhibits JAK1&2 resulting in suppression of cytokine storm. Inhibits AAK1 resulting in cessation of viral cellular entry.
Camostat mesilate	Serine protease TMPRSS2	Supresses the TMPRSS2 thereby inhibiting the priming of S-protein and hinders the viral entry into host cell.
Anakinra	IL-1 receptor	Inhibition of IL-1 receptor leading to suppression of cytokine storm.
Vitamin C	Cytokine storm	Inhibits the efflux of cytokine storm, also acts as antioxidant.
Vitamin D	Cytokine storm	Inhibits the inflammatory cytokine efflux.
Convalescent plasma therapy, Intravenous immunoglobulins.	Inflammatory process	Plasma drawn from COVID-19 recovered patients contains antibodies against SARS-CoV-2 suppresses the inflammatory processes.

The WHO on March 22 2020, started conducting a global megatrial called SOLIDARITY in which active cases of COVID-19 are subjected to standard care or one of four active treatments (remdesivir, chloroquine or hydroxychloroquine, lopinavir/ritonavir, or lopinavir/ritonavir plus interferon beta-1a) [35].

Table 2: WHO megatrial drugs:

DRUG	PEDIATRIC DOSE	ADULT DOSE	ADVERSE DRUG REACTIONS	LAB MONITORING (IN CONDITIONS)
Chloroquine	5mg/kg/PO max. dose-500mg	1gm /PO/ OD for day 1 then 500mg/PO/OD for 4-7 days	Nausea, vomiting, diarrhoea, hepatotoxicity, prolonged QTc interval, ventricular arrhythmias, rash, hypoglycaemia	Monitor ECG, liver enzymes, potassium, magnesium and serum creatinine levels and obtain G6PD test
Hydroxychloroquine	Not recommended for less than 12 years of age	400mg PO BID for one day then 200mg PO BID for 4 days	Retinopathy, rash, QTc prolongation, diarrhoea, haemolysis. hypoglycaemia	Diabetes, Risk for QTc prolongation, obtain G6PD test
Remdesivir	5mg/kg IV infusion on day 1 over 30-120min then 2.5 mg/kg for 10 days	200 mg IV infusion on day 1 for 30-60mins then 100mg infusion for 10days	Nausea, Vomiting, PT and INR prolongation, elevation of ALT and AST	Monitor for liver enzymes, PT and INR levels
Lopinavir/Ritonavir	Not Recommended	200/50mg BID for 14 days Or 400mg/100mg 5ml suspension for 14 days	Nausea, vomiting, diarrhoea, QTc prolongation& hepatotoxicity	Monitor CBC, ECG & LFTs, RFTs
Interferon beta-1a (IFNβ-1a)	8.8-44mcg/SC 48 hrs apart	44mcg SC 48hrs apart	Fever, fatigue, leukopenia, Thrombocytopenia, lymphopenia, headache, rash, thrombophlebitis	Monitor CBC, LFTs

NOTE:PO- per oral, OD- once daily, BID- twice/bis in day, IV- intravenous, SC- subcutaneous, PT- prothrombin, INR- international normalized ratio, ALT- alanine transaminases, AST- aspartate transaminases, LFTs- liver function tests, ECG- electrocardiogram and CBC- complete blood count. The above-mentioneddrugs are only the current FDAEUA recommended ones and doses are not approved they are based on enclosed Pharmacokinetic and pharmacodynamic modelling data (PK/PD).

The therapeutic compatibilities for special population (pregnancy, nursing mothers, paediatrics and geriatrics) are carefully considered based on risks and benefits as there are no approved drugs for COVID-19 and are justified based on CDC guidelines for current clinical management before administration of FDAEUA drugs. Standard of care is the best modality in case of special population as of now.

Table 3: Concomitant medications considered for comorbidities accompanied with COVID-19[33]:

COMMORBIDITIES ALONG WITH COVID-19	CONCOMITANT MEDICATIONS	RECOMMENDED OR NOT RECOMMENDED
Hypertension	Angiotensin converting enzyme inhibitors and angiotensin receptor blockers	Recommended to continue these medications by The American Heart Association and American College of Cardiology.
Patients who are on mechanical ventilation without ARDS.	Corticosteroids	Recommended the use of systemic corticosteroids.
Patients who are on mechanical ventilation with ARDS.	Corticosteroids	Insufficient clinical evidence.

Septic shock	Corticosteroids	Recommended to use low dose of corticosteroids.
Cardiovascular diseases	HMG COA reductase inhibitors	Recommended to use.
Symptomatic relief	Non-steroidal anti-inflammatory drugs	Acetylcysteine is recommended to use. Ibuprofen is not recommended as it is thought to cause over expression of ACE-2 which may worsen COVID-19.

NOTE: The recommendations for drug use are only the hypothesis established by the researchers. So, there is a need for investigating all the assumptionsapart from being interpreted.

VACCINES UNDER CLINICAL TRIALS EXPECTED SOON TO MARKET:
Table 4: Vaccines under development [36]:

VACCINE	DEVELOPED BY	MECHANISM
Ad5-nCoV	Chinese biotech firm Casino biologics	Uses harmless virus known as adenovirus to transport DNA of spike proteins present on SARS-CoV-2
ChAdOx1	Jenner institute and oxford vaccine group	Uses harmless virus to introduce genes that produce the spike proteins inside human body

II. Conclusion

So far, there are no specific enrolled treatments or vaccines endorsed against COVID-19.Further research should essentially focus on active surveillance of these human infecting viruses. Anti-viral interventions and vaccines should also be prepared to combat emerging infectious diseases for future prevention. Stringent rulesin case of domestication and consumption of wildlife are ought to be enacted. CDC recommended measures should be followed to alleviate the community spread, reduce disease impact and to improve outcomes.

References

[1]. CDC.2019 Novel Coronavirus, Wuhan, China. CDC. Available athttps://www.cdc.gov/coronavirus/2019-ncov/about/index.html.January 26, 2020; Accessed: April 27, 2020.
[2]. Li F, Li W, Farzan M, Harrison, SC. Structure of SARS coronavirus spike receptor- binding domain complexed with receptor. Science. 2005; 309(5742):1864–1868.
[3]. Menachery VD, Graham RL, Baric RS. Jumping species-a mechanism for coronavirus persistence and survival Curr Opin Virol. 2017; 23: 1-7.
[4]. Gorbalenva AE. Severe acute respiratory syndrome-related coronavirus- The species and its viruses, a statement of the Coronavirus Study Group. Available at https://doi.org/10.1101/2020.02.07.937862.February 11, 2020; Accessed; April 27, 2020.
[5]. Gallegos A. WHO Declares Public Health Emergency for Novel Coronavirus. Medscape Medical News. Available at https://www.medscape.com/viewarticle/924596. January 30, 2020; Accessed: April 27, 2020.
[6]. WHO Director-General's remarks at the media briefing on 2019-nCoV on 11 February 2020. Available athttps://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020. February 11, 2020; Accessed: April 27, 2020.
[7]. 7. The New York Times. Coronavirus Live Updates: W.H.O. Declares Pandemic as Number of Infected Countries Grows. The New York Times. Available at https://www.nytimes.com/2020/03/11/world/coronavirus-news.html#link-682e5b06. March 11, 2020; Accessed: April 27, 2020.
[8]. Andersen KG, Rambaut A, LipkinWI, *et al.*, The proximal origin of SARS-CoV-2. Nat. Med. 2020; 26:450–452.
[9]. WHO (2020). Novel Coronavirus(2019-nCoV) Situation Report 23.https://www.who.int/docs/default-source/coronaviruse/situation-reports/20200212-sitrep-23-ncov.pdf?sfvrsn=41e9fb78_4.
[10]. Zhou F, Yu T, Du R, *et al*., Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet. 2020 Mar 11.
[11]. CDC.Coronavirus Disease 2019 (COVID-19): People who are at higher risk for severe illness. Centres for Disease Control and Prevention. Available at https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html. Accessed: April 28, 2020.
[12]. Min Jin J, Bai P, He W, *et al*., Gender differences in patients with COVID-19: focus on severity and mortality. Front Pub Hlth. 2020 Apr 29.
[13]. CDC.Symptoms of Coronavirus. CDC. Available at https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html. March 20, 2020; Accessed: April 28, 2020.
[14]. Spinato G, Fabbris C, Polesel J, *et al*., Alterations in Smell or Taste in Mildly Symptomatic Outpatients With SARS-CoV-2 Infection. JAMA. 2020 Apr 22.
[15]. Landa N, Eckert MM, Pascual PF, *et al*., Chilblain like lesions on feet and hand during the COVID-19 pandemic. Int J Dermal. 2020 Apr 24.
[16]. Wu P, Duan F, Luo C, *et al*., Characteristics of ocular findings of patients with coronavirus disease 2019 (COVID-19) in Hubei province, China. JAMA. 2020 Mar 31.
[17]. WHO. Statement on the Second Meeting of the International Health Regulations Emergency Committee Regarding the Outbreak of Novel Coronavirus (2019-nCoV); World Health Organization: Geneva, Switzerland, 30 January ,2020. Available online: https://www.who.int/news-room/detail/30-01-2020-statement-on-the-second-meetingof-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novelcoronavirus-(2019-ncov)Accessed April 28, 2020.
[18]. CDC. 2019 Novel Coronavirus, Wuhan, China: Frequently Asked Questions and Answers. CDC. Available at https://www.cdc.gov/coronavirus/2019-ncov/faq.html. January 27, 2020; Accessed: April 28, 2020.

[19]. Corona virus has mutated into 10 different forms claims study. Available at https://www.businesstoday.in/latest/trends/coronavirus-has-mutated-into-10-different-types-claims-study/story/402254.html. April 28 ,2020; Accessed: April 28, 2020.

[20]. CDC. Emerging Infectious Diseases. Available online at https://wwwnc.cdc.gov/eid/article/26/7/20-0282_article. 07 July, 2020. Accessed on April 30, 2020.

[21]. Canrong WU, Yang L, Yueying Y. *et al.,* Analysis of therapeutic targets for SARS-CoV-2 and discovery of potential drugs by computational methods, Acta Pharmaceutica Sinica B, https://doi.org/10.1016/j.apsb.2020.02.008.

[22]. Zhou P, YangX, Wang X, *et al.,* A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature.2020; 579:270-273

[23]. Nadeem MS, Zamzami MA, Choudhry H, *et al.,* Origin, Potential Therapeutic Targets and Treatment for Coronavirus Disease (COVID-19). Pathogens .2020;9:307.

[24]. Liu C, Zhou Q, Li Y. *et al.,* Research and Development on Therapeutic Agents and Vaccines for COVID-19 and Related Human Coronavirus Diseases. ACS Central Sci. 2020;6 (3):315-331.

[25]. WHO. Detection of 2019 novel coronavirus (2019-nCoV) in suspected human cases by RT-PCR. 2020. Available online: https://www.who.int/health-topics/coronavirus/laboratory-diagnostics-fornovel coronavirus Accessed : April30, 2020.

[26]. RodriguezMA, Tiwari R, Sah R, *et al*., COVID-19, an Emerging Coronavirus Infection: Current Scenario and Recent Developments-An Overview. J. Pure Appl. Microbiol. 2020; 14(1):6150.

[27]. Yu L, Wu S, Hao X, *et al*., Rapid colorimetric detection of COVID-19 coronavirus using a reverse transcriptional loop-mediated isothermal amplification (RT-LAMP) diagnostic plat-form: iLACO. medRxiv 2020.

[28]. New Rutgers Saliva Test for Coronavirus Gets FDA Approval. Rutgers Today. Available at https://www.rutgers.edu/news/new-rutgers-saliva-test-coronavirus-gets-fda-approval. April 13, 2020; Accessed: April 28, 2020.

[29]. COVID-19: Home Pulse Oximetry Could Be Game Changer, Says ER Doc - Medscape - Apr 24, 2020.

[30]. Abott TR, Dhamdhere G, Liu Y, *et al*., Development of CRISPR as an antiviral strategy to combat SARS-CoV-2 and influenza. Cell. 2020 Mar 20.

[31]. Huang C, Wang Y, Li X, *et al*., Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet. 2020 Jan 24.

[32]. Wu C, Chen X, Cai Y, *et al*., Risk Factors Associated with Acute Respiratory Distress Syndrome and Death in Patients with Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020 Mar 13.

[33]. 33.NIH;COVID-19 Treatment Guidelines. Availableonline at https://covid19treatmentguidelines.nih.gov/. Accessed on May 02, 2020.

[34]. WHO R&D Blueprint; Informal consultation on prioritization of candidate therapeutic agents for use in novel coronavirus 2019 infection. Available online athttps://r.search.yahoo.com/_ylt=AwrxhWojIbBeBgQANQ3nHgx.;_ylu=X3oDMTByajVjNzRjBGNG8Dc2czBHBvcwM0BHZ0aWQDBHNlYwNzcg/RV=2/RE=1588629923/RO=10/RU=https%3a%2f%2fapps.who.int%2firis%2fbitstream%2fhandle%2f10665%2f330680%2fWHO-HEO RDBlueprint%2528nCoV%25292020.1eng.pdf%3fua%3d1/RK=2/RS=bYovlPfNrSshNwKm065ggUGFtOI-24 January 2020. Accessed: May 01, 2020.

[35]. Solidarity clinical trial for COVID-19 treatments. World Health Organization. Available at https://www.who.int/emergencies/diseases/novel-coronavirus-2019/global-research-on-novel coronavirus-2019-ncov/solidarity-clinical-trial-for-covid-19-treatments. Accessed: Apr 29, 2020.

[36]. A study of a candidate COVID-19 Vaccine. Available at https://clinicaltrials.gov/ct2/show/NCT04324606. Accessed: May 02,2020.

Shravani Komuravelly, et. al. "Receptors Expression and Treatment Modalities of Corona Virus Disease 2019."*IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)*, 19(5), 2020, pp. 35-40.