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Clinical Evidence of Possible Drug Targets and Pharmacological Management of Novel Covid-19: The World Threatening Virus

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ABSTRACT

Introduction: According WHO (world health organization) viral infections (CoVID-19) spread rapidly and causing an serious issue to whole world. Coronaviruses are the major pathogens that primarily targets the human respiratory system. Previous outbreaks of coronaviruses (Covs) include the severe acute respiratory syndrome (SARS)-cov and the Middle East respiratory syndrome (MERS)-Cov which caused major impact on public health and lead to high mortality rate. The first case of covid-19 was reported in patients with pneumonia [3] in china.

Aim & Objectives: To study clinical evidence of possible drug targets and pharmacological management on covid-19.

Methodology: It is systematic reviews of covid-19 pandemic crisis.

Discussion and Conclusion: After understanding the Viral Genome of SARS-CoV with the help of previous Studies, here we suggest the hypothetical targets to destroy CoVID-19 which includes- Spike protein binding inhibition, Inhibiting Frame shifting (ORF`s) and Inhibition of nsp10/16 complex formation.

As per our study we also conclude that HCQ effectively inhibited virus entry into the host cell, through changing the glycosylation of ACE-2 receptor and spike proteins. So before advice HCQ one must consider its contraindications (Retinopathy, Cardiac abnormalities, G6PD deficiency, etc). Vitamin-C shows vital role in Preventing respiratory tract infections (CoVID-19), so levels of Vitamin-C to be maintained in patients. Iron and zinc supplements to be given as they boosts immune system and inhibits viral infections respectively. Few antiviral drugs -lopinavir/ritonavir, Remdesivir shown better out comes in CoVID-19.

KEYWORDS

Corona Virus, SARSCoV-2, Viral Replication, Possible Drug Targets, Hydroxychloroquine, Vitamin-c, Anti-Viral drugs

INTRODUCTION

According WHO (World Health Organization), viral infections spread rapidly and cause serious issue to the public. One of such Viral infections is COVID-19, which is threatening whole world.(1) Probably it's a question and challenge to the survival of the mankind on this planet Earth. Coronaviruses (CoVs) are the largest group of viruses belonging to the Subfamily - Coronaviridae of Nidovirales order and Coronaviridae are further consists four groups, the alpha, beta, gamma and delta coronaviruses. The present CoVID-19/ SARS CoV-2 is beta Corona Virus. Most of Human Corona Viruses cause Severe Acute Respiratory Syndrome (SARS-CoV). As SARS-CoV-2 have greater binding affinity with ACE2 [2]. Respiratory distress is the common most symptom observed with this Virus causing lethal effect to the Human Lungs. Since there are no specific antiviral drugs till date, It is important to understand the structural and functional proteins of the Virus.

EPIDEMIOLOGY OF COVID-19

Coronavirus is one of the major pathogens that primarily targets the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which caused major impact on public Health and lead to high Mortality Rate. The First case of CoVID-19 was reported in Wuhan, China in December 2019

from patients with pneumonia [3]. This 2019 Novel Virus nature is Human-Human transmission and was rapid than that of previous Outbreak of SARS-CoV in 2003 and MERS-CoV in 2012. Almost 153, 517 CoVID-19 cases were confirmed across the Globe.143 different countries got effected by March 15, 2019. Hence it was declared as Pandemic Disease by WHO [4].

Majority of cases were reported in China (81,639) with mortality rate 4% [5]. It was believed that the virus was suspect originated from Wet animal whole sale market, Wuhan, China [6]. Previously, SARS-CoV originated through Bats in Guagdong, China and affected 8,096 cases across 30 countries which lead to 774 deaths in 2003. Later in 2012 another outbreak was MERS-CoV, originated though Camel in Saudi Arabia and effected about 2,500 cases which lead to 850 deaths. Whereas, SARS-CoV-2(CoVID-19) Out break drastically effected 1,119,744 cases and 59,245 deaths across the Word as of 4th April, 2020 and still the number Counts [7]. United States and Italy are becoming biggest disease outbreak after China. As per the Rup Lal, scientist in TERI (The Energy and Resources Institute), made in depth genomic Analysis of SARS-CoV-2 Virus and stated that the Viral Strain in India is relatively less Virulent than the Viral strain which effected Italy and United States [8].

PATHOPHYSIOLOGY

Current virus which is threatening the world is COVID-19, which belongs to order Coronaviridae. The nomenclature of COVID-19 is given WHO which can be expanded as CO-corona, VI- virus, D- Disease and 19 was given as its outbreak is in 2019 in Wuhan region CoVs consists of positive single strand RNA, these are known as largest RNA viruses (30 kb in length) with a 5′-cap structure and 3′-poly-A tail [11].

Transcription: Transcription occurs through Replication Transcription Complex (RTC), which is organized by double membrane vesicles and also through synthesis of sub-genomic RNAs sequences. Termination of transcription occurs at Regulatory sequences present between Open reading frames. These open reading sequences acts as templets for the production of Subgenomic m-RNA.

In **Cov genome**, 6 open reading frames are present. Frame shifting occurs between ORF1a, ORF1b which leads for the production of pp1a,pp1ab polyproteins are formed. Once pp1a,pp1ab polyproteinswere formed, they are processed by Virally encoded "Chymotrypsin like Protease(3CLpro)"or "Main Protease (Mpro)" and "Papain like proteases", thus producing 16nsp (16 non-structured proteins). Few other ORFs encode for structural proteins, including spike, membrane, envelope, and nucleocapsid proteins [12].

CoVs contains glycoprotein spikes on their outer coat which is composed of two subunits S1 and S2. These spikes acts as domain to link with the host cells. In similar fashion SARS-CoV-2 Virus also contain S2 subunit. These S2 sub-unit contains a fusion peptide (a transmembrane domain and Cytoplasmic domain) which binds to the host cells.

- **Attack of covid-19 to the host cell:**

For our understanding, CoVID-19 attacks to the host cell as been theoritically simplified by the following steps

STEP 1:

Attachment of the Virus to Host: SARCoV have S2 spike proteins [14] which consists of Receptor Binding Domain (RBD) at C-terminal. This RBD of SARCoV use Angiotensin Converting Enzyme-2 (ACE-2) of host cell as receptor. Thus it gets attached to the Host cell (Human). It is unclear that why peptidases are used, as entry occurs even in the absence of the enzymatic domain of these proteins.

Recently identified MERS-CoV binds to dipeptidyl-peptidase 4 (DPP4) to gain entry into human cells [39]. But DPP4 binding is not observed in current SARCoV (CoVID-19).

STEP 2:

Fusion of Viral and Cellular membrane of Host: Proteolytic Cleavage of S2 protein spike must occurs in order to get access to Host cell Cytosol. S2 portion of protein gets separated from RBD (Fusion domain) by CAPthesin, TMPRRS-2 and other proteases¬. Cleavage of S2 exposes a fusion peptide inserts into membrane followed by the joining of heptad repeats in S2 forming a six helix bundle. This formation of bundle allows for mixing of Viral and cellular membranes, which ultimately results in the release of viral genome into the cytoplasm [15,16].

STEP 3:

Genome Replication: Positive-Sense Viral RNA is identical to viral mRNA and thus can be immediately translated into protein by protein by the Host Cell. Replication of Novel-Corona Virus is not clear but it is somewhat similar to previous beta-Corona Viruses like SARS CoV. This Step Virus develops Polyproteins; For the virus utilizes slippery sequence (5`-UUUAAC-3') for its replication. It also use RNA pseudo knot, which is responsible for the ribosomal frame shifting from rep1a to rep1b (ORF`s) which ultimately results in the formation of Poly proteins like PP1ab and PP1a [17].

Once polyproteins are formed they must under cleavage process, to ensure that corona virus encodes proteases that could cleave replicase-Polyproteins. SARSCoV encodes PLpro (papain-like proteases) within nsp3. PLpro cleaves nsp1/2, nsp2/3, nsp3/4 and thus many nsp`s are formed. These nsp`s assembly into RTC (Relicase-Transcriptase Complex). RTC creates suitable environment for RNA synthesis, responsible for formation of sub-genomic RNAs.

Novel aspect of coronavirus replication is how the leader and body TRS segments fuse during production of sub-genomic RNAs. The current model proposes that the RdRp (RNA dependent RNA polymerase) pauses at any one of the body TRS sequences (TRS-B); following this pause the RdRp either continues elongation to the next TRS (Transcription Regulatory sequences) or it switches to amplifying the leader sequence at the 5′ end of the genome guided by complementarily of the TRS-B to the leader TRS (TRS-L). Many evidences currently support this model, including the presence of anti-leader sequence at the 3′ end of the negative- strand sub-genomic RNAs [18].

Finally, coronaviruses are also known for their ability to recombine using both homologous and non-homologous recombination [19]. The ability of these viruses to recombine is tied to the strand switching ability of the RdRp. Recombination likely plays a prominent role in viral evolution and is the basis for targeted RNA recombination, a reverse genetics tool used to engineer viral recombinants at the 3′ end of the genome.

STEP 4:

Assembly & Maturation: Virus contains S (Spike), E (Envolope), M (Membrane) and these are encased by N protein. N protein enhances VLP`s(Viral like Protein) formation and helps in Fusion of encapsulated genomes into ERGIC (endoplasmic reticulum–Golgi intermediate compartment) enhances viral envelope. M protein interactions with E protein, results in VLP`s formation; M protein also provide the impetus for envelope maturation. M Protein interacts and binds with nucleocapsid, these interaction have been mapped C-terminus of the endodomain of M with CTD of the N-protein [20] and thus promotes the completion of viral assembly.

E protein plays the role in inducing Membrane curvature and also have key role in promoting viral release by altering the host response pathway [21].

N protein selectively packs only positive sense full length genomes among the many different RNA species produced during infection. A packaging signal for MHV has been identified in the nsp15 coding sequence. A packing signal is at nsp15 coding sequence.

STEP 5:

Release: Following assembly, virions are transported to the cell surface in vesicles and released by exocytosis. S protein that does not get assembled into virions transits to the cell surface where it mediates cell–cell fusion between infected cells and adjacent,

uninfected cells. This leads to the formation of giant, multinucleated cells, which allows the virus to spread within an infected organism without being detected or neutralized by virus-specific antibodies.

- **Human Immune Respose to Virus:** SARS-CoV infects epithelial cells in Lungs (ACE). SARS-CoV-2 exploits the endogenous transcriptional machinery of alveolar cells to replicate itself and spreads through the entire lung [22]

It is capable of entering into macrophages and dentric cells [23,24] and causes severe infection. Despite of infection, these cells plays an important role in inducing Pro-Inflammatory Cytokines and Chemokines [25]. In blood samples of CoVID-19 patients, significantly high levels of cytokines and Chemokines were noted- that includes IL7, IL8, IL9, IL10, IL1RA, IL1-β, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα [26]. COVID-19 binds to ACE-2,which is not only expressed in lungs but has been reported in other organs includes-Kidney, Heart, Gut [27] and could be the reason for the high mortality rate in patients with multiple comorbidites [28].

DIAGNOSITIC PARAMETERS

Clinical Manifestation

Patients infected with CoVID-19 show common symptoms such as dry cough, High grade fever, fatigue, dyspnea and with or without nasal congestion, runny nose or other upper respiratory symptoms.

Physical Examination

Some patients have mild symptoms may not present positive signs, so in severe condition may have shortness of breath, moist rales in lungs, weakened breath sounds, dullness in percussion, and increased or decreased tactile speech tremor.

Hematology Examination

In the early stage of CoVID-19, the leukocytic count may be decrease or will be normal. But the lymphocytes or CD4 and CD8 T cells may significantly decreased, So in such conditions patients were recommend to recheck the blood routine changes after 3 days.

Laboratory Tests

The COVID-19 nucleic acid detection or Accurate RNA detection of COVID-19. The RNA of COVID-19 positive in the throat swab sampling or other respiratory tract sampling by fluorescence quantitative PCR method, especially that from multiple samples and detection kits.

There are other laboratory tests such as blood gas analysis, myocardial enzyme (myoglobin), erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Procalcitonin (PCT), lactate, D-dimer, coagulation image, urine routine test, inflammatory factors (interleukin(IL)-6, IL-10, TNF - α), complement, anti-acid staining and also liver and kidney function tests were needed in few cases.

Blood gas analysis play a key role to judge the oxygenation of moderately-illed and severe patients. The increase of lactic acid, it is feasible to screen the patients with high-risk of oxygenation disorder. Some infected patients have increased liver enzymes, muscle enzyme, ESR and myoglobin. The detection of CRP and PCT is of certain value is useful to distinguish whether there was bacterial infection in the lung. D-dimer of most severe patients was significantly increased in this epidemic, with frequent clotting disorders and microthrombotic formation in peripheral blood [29].

Vital signs to be monitored in CoVID-19 Patients

- Heart rate, pulse oxygen saturation, respiratory rate, blood pressure) and given supportive treatment to ensure sufficient energy intake and balance for water, electrolytes, acid-base levels and other internal environment factors (Strong recommendation).
- The patient should be monitored for blood routine, CRP, PCT, organ function (liver enzyme, bilirubin, myocardial enzyme, serum creatinine, urea nitrogen, Urine volume, etc.), coagulation function, arterial blood gas analysis and chest imaging (Strong recommendation).
- If necessary patient should be supported oxygen therapy, including nasal catheter, mask oxygen, High Flow Nasal Oxygen therapy (HFNO), Non-invasive Ventilation (NIV) or invasive mechanical ventilation (Strong recommendation) [29].

TREATMENT

At present, there is no evidence from RCT to support specific drug treatment against the new coronavirus in suspected or confirmed cases. In present scenario the Suspected and confirmed cases need to be treated in hospitals with effective isolation and protection conditions. Critical cases with severe respiratory infections, respiratory distress, hypoxaemia or shock hypoxic respiratory failure-need an immediate ICU assistance as soon as possible and respiratory support to be provided with HFNO or NIV.

PHARMACOLOGICAL AGENTS AND THEIR EFFECT ON COVID-19

Hydroxychloroquine (or) Chloroquine:

Chloroquine (CQ)[N4-(7-Chloro-4-quinolinyl)-N1,N1-diethyl-1,4-pentanediamine] has been used to treat malaria and amebiasis since many years. However, Plasmodium falciparum developed widespread resistance to it, and with the development of new antimalarials, it has become a choice for the pro-phylaxis of malaria. In addition, an overdose of CQ can cause acute poisoning and death. In the past years, due to infrequent utilization of CQ in clinical practice.

Hydroxychloroquine (HCQ) sulfate, a derivative of CQ, was first synthesized in 1946 by introducing a hydroxyl group into CQ and was demonstrated to be much less toxic than CQ as shown in animal studies. More importantly, HCQ is still widely available to treat auto- immune diseases, such as systemic lupus erythematosus and rheumatoid arthritis till today. Since CQ and HCQ share similar chemical structures and mechanisms of acting as a weak base and immunomodulator, it is easy to conjure up the idea that HCQ may be a potent candidate to treat infection by SARS-CoV-2.

Mechanism of Action

CQ and HCQ are weak bases that are known to elevate the pH of acidic intracellular organelles, such as endosomes/lysosomes, essential for membrane fusion. In addition, CQ could inhibit SARS-CoV entry through changing the glycosylation of ACE2 receptor and spike protein. Many Experiments and Studies, confirmed that HCQ effectively inhibited the entry step (inhibiting virus entry), as well as the post-entry stages of SARS-CoV-2. Oral absorption of CQ and HCQ in humans is very efficient. HCQ sulfate could generate serum levels of 1.4-1.5 μ min humans. Therefore, with a safe dosage, HCQ concentration in the above tissues is likely to be achieved to inhibit SARS-CoV-2 infection.

Contraindications

But when we assess the risk and benefit ratio of loosing life with COVID-19 that of contraindication as per literature includes Retinopathy, Myocardial toxicity or myocardial dysfunction, QT interval prolongation, ventricular arrhythmia, Atrioventricular block, G6PD deficiency, Pulmonary hypertension, Hypersensitivity reaction to Hydroxychloroquine or Chloroquine, , Breastfeeding, Pregnant, Not recommended <15 years Age Groups.

Pharmacokinetics

HCQ-Bioavailability is Complete and Rapid Absorption,1-3 hours of peak plasma time, half life 32-50 days, Protein bound: 55%, Excretion: urine 60%

Recommended Dose for Empiric Use of Hydroxychloroquine for Prophylaxis of Sars-Cov-2 Infection:

- ✓ Asymptomatic healthcare workers involved in the care of suspected or confirmed cases of COVID-19: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 7 weeks; to be taken with meals.

- ✓ Asymptomatic household contacts of laboratory confirmed cases: 400 mg twice a day on Day 1, followed by 400 mg once weekly for next 3 weeks; to be taken with meals (ICMR) [30].

LOPINAVIR/RITONAVIR

The lopinavir-ritonavir combination is approved for AIDS treatment in several countries. Both drugs are protease inhibitors, but ritonavir is also a cytochrome P450 and GP inhibitor.

Lopinavir/ritonavir alone or in combination with antiviral produced certain benefits in the treatment of SARS and MERS, such as reducing the incidence or mortality of ARDS. A recently systematic review showed that lopinavir/ritonavir's anti-coronavirus effect was mainly reducing patient mortality and reduced glucocorticoid consumption. Real-world study stills need to further explore the clinical effects of its early use in 2019-nCoV infected pneumonia [31].

REMDESIVIR

A recent paper reported an inhibitor effect of Remdesivir **(a new antiviral drug)** and Chloroquine **(antimalarial drug)** on the growth of SARS-CoV-2 in vitro, [1] and an early clinical trial conducted in COVID-19 patients of China, showed that Chloroquine had a significant effect, both in terms of viral clearance and clinical outcome, when comparing to controls groups. Chinese experts recommend that patients diagnosed as mild, moderate and severe cases of COVID-19 pneumonia and without contraindications to Chloroquine, be treated with 500 mg Chloroquine twice a day for ten days [32].

CORTICOSTEROID THERAPY

The use of corticosteroids for severe ARDS is controversial. But Methylprednisolone can be used as appropriate for patients with rapid disease progression or severe illness. According to the severity of the disease, 40 to 80 mg of Methylprednisolone per day (not exceed 2 mg/kg/day).

SARS management related researches showed that timely use of non-invasive continuous positive airway pressure and corticosteroids is an effective strategy for increased lung shadows and increased dyspnea. Appropriate use of glucocorticoids is able to significantly improve the clinical symptoms of patients with SARS, reduce the degree of disease progression, and accelerate the absorption of lung lesions; but it cannot shorten the length of hospital stay.

H2 RECEPTOR ANTAGONISTS OR PROTON PUMP INHIBITORS

These drugs are Reduce the incidence of stress ulcers and gastrointestinal bleeding risk factors. The risk factors for gastrointestinal bleeding include mechanical ventilation ≥48 hours, coagulation dysfunction, renal replacement therapy, liver disease, various complications, and a higher score of organ failure [33]. So when there is a need to support CoVID-19 patient with mechanical ventilation, we must start these drugs prophylactically.

NUTRITIONAL SUPPORT

Inpatients are screened for nutrition risk based on the NRS **(Nutritional risk screening-2002)** score when they are admitted to the hospital. The recommended plan for patients with different nutrition risk scores are as follows, if the total score is >3 points, it is recommended carbohydrate 25-30 kcal / (kg.d) and the protein mass are 1.5 g / (kg.d).

A) **Iron** is one of the minerals in the human body. It is one of the components of hemoglobin, the substance in red blood cells that helps blood carry oxygen throughout the body. Iron provides the energy and immune boosting.

B) **Zinc** is an essential micro nutrient that plays a crucial role in a majority of the life-enabling enzymatic processes our body. It has the ability to regulate the immune system and its innate antimicrobial activity. White blood cells mainly defense against viral infections. Zinc supplementation has been shown to increase white blood cell counts in zinc-deficient patients but also increases the immune response in healthy patients. It also has an intrinsic antiviral activity that extends to the corona family of viruses. In vitro (cell) studies have shown that zinc inhibits viral replication by blocking a key viral enzyme utilized for replication in host cells, RNA polymerase [34].

C) **Vitamin C**, also known as Ascorbic Acid and Ascorbate, it is a water-soluble vitamin that neutralizes a variety of **reactive oxygen species** and recycles important cellular **antioxidants**.

It's an essential nutrient involved in the repair of tissue and the enzymatic production of certain neurotransmitters. Vitamin C has antioxidant activity and it may reduce oxidative stress and inflammation, effects that improve vasopressor synthesis, enhance immune cell function, improve endovascular function, and provide epigenetic immunologic modifications.

Deficiency of Ascorbic acid levels associated with increased susceptibility to infections and an increased risk of pneumonia.

In present matter of discussion, Most of patient have Vitamin C Levels were drop in acute respiratory infection, so in COVID-19 patients drop dramatically when they suffer sepsis an inflammatory response that occurs when their bodies over react to infection.

As per few studies conducted in COVID-19 with Vitamin-C shown better results with the dosage of 100-200 mg/kg/day of treatment [39]. So, WHO suggested the Adult dose about 400-1000 mg/day.

DISCUSSION

Few Studies done by Bosch BJ *et al*., found that **vitamin C supplement** used to eliminate alveolar fluid by preventing the activation neutrophilsand reducing alveolar epithelial water channel damage. Vitamin C can prevent the formation of neutrophil extracellular traps, it is a biological event of vascular injury caused by neutrophil activation. Vitamin C can effectively decrease the duration of the common cold and Few extreme conditions (Athletes, exercises) prevent the common cold. It is also has a certain protective effect on influenza patients, few studies found that vitamin C deficiency is related to the increased risk and severity of influenza infections [35].

Vitamin C changes susceptibility to various bacterial and viral infections, few controlled trials have shown consistently that the duration and severity of common cold episodes are reduced in the vitamin C Subjects, so it indicating that viral respiratory infections in subjects are affected by vitamin C levels. Few standard evidence indicating that vitamin C may affected in pneumonia patients. In particular some studies with subjects (human) reported a significantly lower incidence of pneumonia in vitamin C-supplemented groups. Vitamin C may affect susceptibility to lower respiratory tract infections (COVID-19) under certain conditions. The possibility that vitamin C affects severe viral respiratory tract infections would seem in further studies and especially the recent SARS Epidemic [36].

A recent paper Sandro G *et al*., reported CQ and HCQ used as antimalarial drugs. Sandro G study said that CQ or HCQ have antiviral effects against HIV, it is know as by inhibiting virus entry into host cells. Also mechanism of action related to the post-translation alteration of newly synthesized proteins via glycosylation inhibition.

In a recent trial with patients on COVID-19 treatment 100% of patients treated with Hydroxychloroquine in combination with **azithromycin** (Macrolide antibiotic) were virologically cured comparing with 57.1% in subjects (Test dose) treated with single molecule of Hydroxychloroquine, and 12.5% in the subjects(control group). Presently Chloroquine and Hydroxychloroquine will be tested in subjects with pneumonia caused by COVID-19 and Chloroquine as preventative medicine for COVID-19 [39].

Based on this consideration and some preliminary (pre-published) result from Gautret study said that **Chloroquine and Hydroxychloroquine** treatment effected noticeable changes in the number and size/morphology of EEs (Early Endosomes) and EL (Endolysosomes). In this some cells are untreated, mostly EEs were very smaller than ELs. **Chloroquine and Hydroxychloroquine** treated cells showed that abnormally enlarged EE vesicles were

observed, few cells are larger than ELs in the untreated cells. In this study previous reports observed, treatment with **Chloroquine** induced the formation of expanded cytoplasmic vesicles. In the EE vesicles describe, virions (red) were localized around the membrane (green) of the vesicle. **Chloroquine** treatment did not cause obvious changes in the number and size of ELs. The regular vesicle structure showed to be disrupted, at least partially. **Hydroxychloroquine**-treated cells, the size and number of ELs increased significantly [38].

FUTURE PROSPECTIVES OF DRUG TARGET ON COVID-19

As we mentioned the COVID-19 structure and replication here we are presenting our hypothesis on drug targets. Anyways further research as to be done for drug discovery. Our hypothesis as follows:

- **Target-1:** At binding level **Spike proteins**, S2 sub-unit of SARS-CoV-2 binds to host cells. So, we can target the possible antiviral drugs on this S2 sub-unit. But these binding domain-presents 40% Amino acids to identify as that of other SARS-CoVS.
- **Target-2:** Structural elements like **ORF-3b**, that has no homology with that of SARs-CoVs. And few **secreted proteins** (encoded by ORF8), which is structurally different from those SARS-CoV-2.
- **Novel Target-3 (New potential drug target):** CSGID scientists, a lead investigator Mrs. Karla Satchel and team, mapped atomic structure of SARS-CoV-2 particularly its two important proteins, complex of called nsp10/16. It is the key point for drug discovery because this protein is absolutely essential for the virus to replicate. These two proteins modify the genetic material of SARS-CoV-2 to make it look like more human RNA, allowing it to avoid host antiviral defenses and giving time to multiply. If a drug can be developed to inhibit nsp-10/nsp-16, the immune system should be able to detect the virus and eradicate it faster. The nsp10/nsp16 protein complex is called as an "RNA methyl transferase (MTase)" As per previous research conducted on SAR's, it was noticed that the association of these two pieces (nsp-10/nsp16) together is required to make functional proteins. So, if we could discover the drugs, which can inhibit the fusion of nsp-10 and nsp16. So that the virus becomes incapable to produce its functional proteins, ultimately Virus can be destroyed [13].
- Few Other Protein Targets: As per Adrzej Joachimiak (University of Chicago) and Godzik's Bio-informatic team (North Western university) revealed few more protein targets which includes nsp-15 endonuclease, nsp-3 ADP ribose Phosphate, nsp-9 replicase.

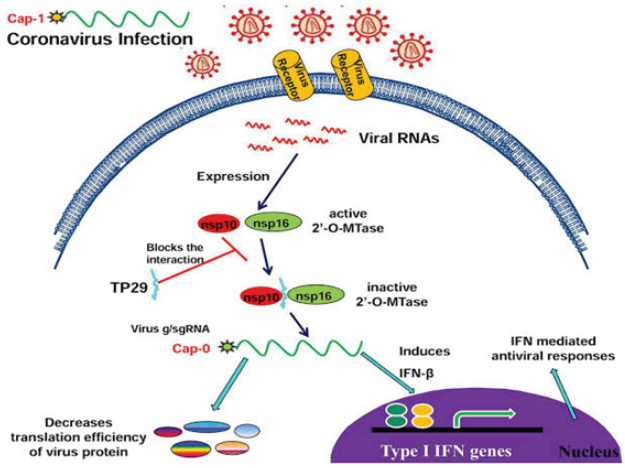

Figure 1: Diagrammatic representation -Hypothesis for mechanism of Peptide-29 in inhibiting the formation of nsp-10/nsp-16 complex, decreasing the translation efficacy of viral RNAs [13]

CONCLUSION

After understanding the Viral Genome of SARS-CoV with the help of previous Studies, here we suggest the hypothetical targets to destroy CoVID-19 which includes- Spike protein binding inhibition, Inhibiting Frame shifting (ORF`s) and Inhibition of nsp10/16 complex formation.

As per our study we also conclude that HCQ effectively inhibited virus entry into the host cell, through changing the glycosylation of ACE-2 receptor and spike proteins. So before advice HCQ one must consider its contraindications (Retinopathy, Cardiac abnormalities, G6PD deficiency, etc). Vitamin-C shows vital role in Preventing respiratory tract infections (Covid-19), so levels of Vitamin-C to be maintained in patients. Iron and zinc supplements to be given as they boosts immune system and inhibits viral infections respectively. Few antiviral drugs -lopinavir/ritonavir, Remdesivir shown better out comes in Covid-19.

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Conflicts of Interest: NIL.

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