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Insight into the COVID-19 Treatment

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ABSTRACT:
Corona viruses are a group of enveloped, non segmented, single-stranded, and positive-sense RNA genomes, There are seven known sorts of corona virus that influence people. Coronavirus disease (COVID-19) is an infectious disease caused by a new virus. The disease causes respiratory illness with symptoms such as a cough, fever, and in more severe cases, difficulty in breathing. In this review good deal of information about Corona viruses are given including its spreading history, properties, facts, drugs and prevention.
KEYWORDS: Corona, RNA, Viruses, Enveloped, Infectious.

INTRODUCTION:

Corona virus found to be the life threatening and disastrous, it is spreading around the world instantaneously. Corona viruses are aggregate of contamination's that cause infirmity reaching out from the typical infection to continuously extraordinary diseases, for instance, "Center East Respiratory Syndrome" (MERS-CoV) and "Genuine Acute Respiratory Syndrome"(SARS-CoV). Regular symptoms of disease incorporate respiratory side effects, fever, vomit, and breathing troubles. Sometimes, the disease can cause pneumonia, kidney disappointment and even death. Corona viruses are zoonotic, that literally means they are transmitted between animals and People. The COVID-19 virus infects people of all ages. However, evidence to date suggests that two groups of people are at a higher risk of getting a severe COVID-19 disease, these are older people, and those with underlying medical conditions [WHO, 2020]. Detailed investigations found that SARS-CoV which is responsible for severe acute respiratory syndrome was transmitted from bats to humans and MERS-CoV from dromedary camels to humans. It can be simple for an infection to cause a species to species jump. Couple of known corona viruses are hovering in animals that have not yet corrupted individuals. There are seven known sorts of corona virus that influence people for example 229E (alpha coronavirus), NL63 (alpha coronavirus), OC43 (beta coronavirus), HKU1 (beta coronavirus), MERS-CoV (the beta coronavirus that causes Middle East Respiratory Syndrome, or MERS), SARS-CoV (the beta coronavirus that causes serious intense respiratory disorder, or SARS), SARS-CoV-2 (The novel coronavirus that causes coronavirus disease-2019) [NCBI] in which the Corona Virus Disease-2019 is recent subject to debate on.

Structure:

Spherical or pleomorphic enveloped particles containing single-stranded (positive-sense) RNA associated with a nucleoprotein within a capsid comprised of matrix protein. The envelope bears club-shaped glycoprotein projections. The glycoproteins are liable for connection to the host cell and furthermore, convey the primary antigenic epitopes, especially the epitopes perceived by killing antibodies. [NCBI, 2020].

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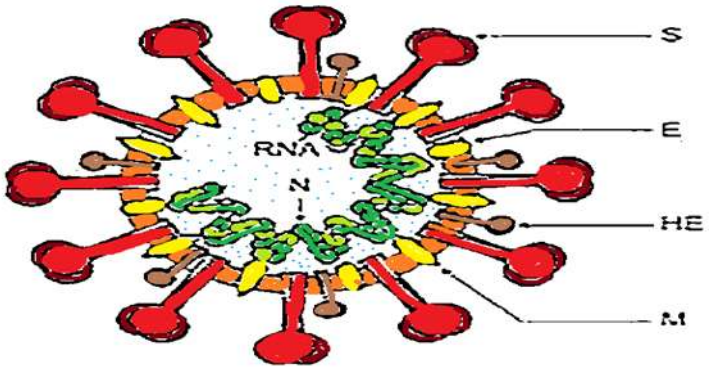

S: Spike
E: Envelope glycoproteins
HE: Hemagglutinin esterase
M: Membrane
N: Nucleocapsid.

Fig 1.1: Corona virus structure.

Symptoms:

Symptoms can include fever, cough and shortness of breath. In more severe cases, infection can cause pneumonia or breathing difficulties. More rarely, the disease can be fatal. These symptoms are similar to the flu (influenza) or the common cold, which are a lot more common than COVID-19. This is why testing is required to confirm if someone has COVID-19 (W.H.O. 2020)

Prevention:

Steps to be taken to protect ourselves from the Corona virus disease are as follows

Clean our hands often:

- Wash your hands frequently with cleanser and water particularly after you have been in an open spot, hacking, or sniffling.
- On the off chance that cleanser and water are not promptly accessible, clean your hands with a hand sanitizer that contains 60% alcohol.
- Avoid touching your eyes, nose, and mouth with unwashed hands.

Avoid close contact:

- Avoid close contact with people who are sick.
- Put distance between yourself and other people if Corona Virus Disease is spreading in your community. This becomes important for people who are at higher risk of getting very sick.

Steps to protect others:

- Stay home if you are sick.
- Covering our mouth when coughing.
- Cover coughs and sneezes.
- Throw used tissues in the trash.
- Immediately wash your hands with soap and water for at least 20 seconds.
- Wear a facemask if you are sick.
- If you are sick: You should wear a facemask when you are around other people (e.g., sharing a room or vehicle) and before you enter a healthcare provider's office.
- Cleaning a counter.
- Clean and disinfect.
- Clean and disinfect frequently touched surfaces daily.
- If surfaces are dirty, clean them: Use detergent or soap and water prior to disinfection.

[WHO REPORT 2020].

The drug's against Covid19 disease:

1) Hydroxychloroquine and Chloroquine

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Hydroxychloroquine (HCQ) sulfate is derived from chloroquine. The hydroxyl group present upon Chloroquine (CQ). Chloroquine shows a broad range of properties in case of bacterial, parasitic, fungal, protozoal, and viral infections [1]. Hydroxychloroquine is more safer than chloroquine [2]. Chloroquine it was first synthesized in 1934. This drug is useful in the prevention and treatment of malaria [3]. The chemical formula of Hydroxychloroquine is C18H36ClN30[4].

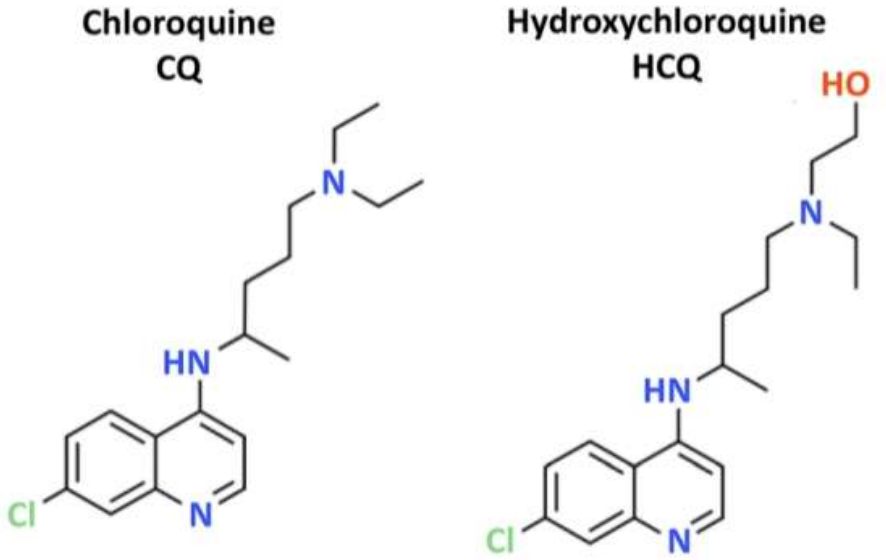

Fig. 1 The chemical structure of Chloroquine and Hydroxychloroquine [5].

2) Dexamethasone

Dexamethasone is a synthetic corticosteroid drug. Corticosteroid consist of mineralocorticoid and glucocorticoid. These are effectively used in several kinds of diseases and their symptoms. Dexamethasone shows various properties like odorless, white, and crystalline powder. Dexamethasone is a steroid compound and insoluble in water. The molecular weight of dexamethasone is 392.47 Da. Their chemical formula is C22H29FO5. Dexamethasone is also known as 1-dihydro-9α-fluoro-16α-methyl hydrocortisone [6]. It shows a broad-spectrum activity. This drug is approximately30 times more powerful and its action is a long period (2-3 days) compared to cortisone [7]. Dexamethasone is the first drug that has the potency to save the life of patients against COVID-19 [8].

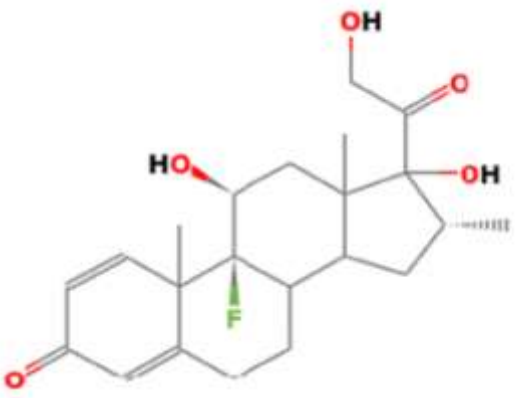

Fig. 2 The Chemical structure of Dexamethasone [6].

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3) Lopinavir / Ritonavir

The chemical formula of Lopinavir is C37H48N4O5 and Ritonavir is C37H48N605S2 [4]. Lopinavir is an antiretroviral protease inhibitor [9]. The Lopinavir is used in combination with Ritonavir in HIV infection therapy and prevention. The Lopinavir and Ritonavir combination is helpful against the COVID-19 that decreases the viral load and improves the conditions [10]. Ritonavir is a powerful enzyme inhibitor it is important for lopinavir metabolism and its co-administration increase lopinavir exposure and enhances antiviral activity [11].

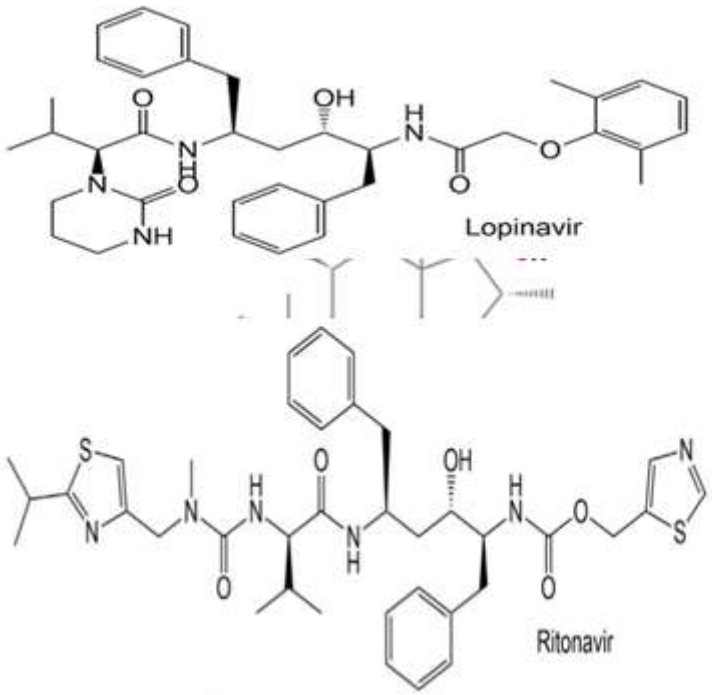

Fig. 3 The Chemical structure of Lopinavir and Ritonavir [10].

4) Favipiravir

Favipiravir is a purine base analog and is included in the site of guanine or adenine [12]. It is a selective and powerful inhibitor of RNA-dependent RNA Polymerase of the many viruses that contains RNA as a genome.[10]. The favipiravir is also known as T-705. It acts as an

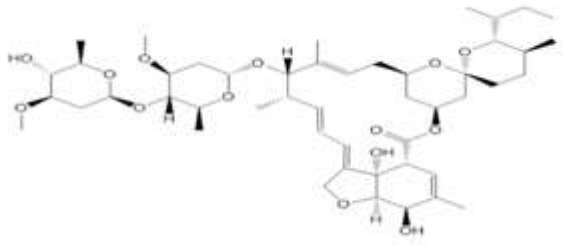

Fig. 4 The Chemical structure of Favipiravir [10].

antiviral agent. The chemical name of favipiravir is 6-Fluoro-3-oxo-3,4-dihydropyridine-2-carboxamide [13].

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5) Ivermectin

Ivermectin is included in the class of drugs known as 'avermectins'. It contains the 10-membered macrocyclic lactone compounds [14]. Ivermectin shows a broad range of anti-parasitic activity. The Ivermectin also has a broad range of antiviral activity against viruses [15].

Fig. 5 The chemical structure of Ivermectin [16].

6) Colchicine

Colchicine is an alkaloid compound. The chemical formula of colchicine is $C_{22}H_{35}NO_6$. The chemical name is N-[(7S)-5,6,7,9-tetrahydro-1,2,3,10-tetra methoxy-9-oxybenzone(a)heptalen-7-yl)acetamide] [17]. It is a neutral lipophilic tricyclic alkaloid, the main property consists of a trimethoxy phenyl ring, a 7-membered ring, and in the seventh position acetamide is present and a tropolonic ring. The colchicine is also showing property such as anti-inflammatory and antiviral [18].

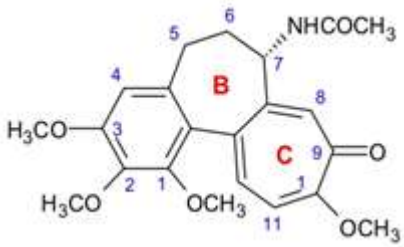

Fig. 6 The chemical structure is colchicine [18].

7) Remdesivir

Remdesivir is a monophosphoramidate prodrug and its molecular weight is 602.6 g/mol. The molecular formula is $C_{27}H_{35}N_6O_8P$. It is designed as a GS-5754 [10]. Remdesivir is a nucleotide analog. It produces an antiviral activity in the case of RNA viruses like a respiratory syncytial virus, Lassa virus and Coronaviruses include SARS-CoV and MERS-CoV[19].

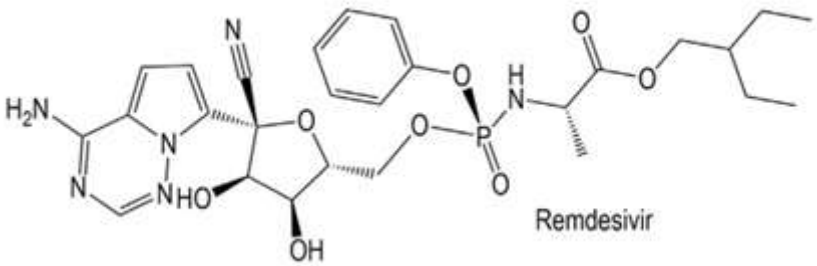

Fig. 7 The chemical structure of Remdesivir [10].

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8) Azithromycin

Azithromycin is included in the class of macrolides. It shows a bacteriostatic activity [20]. They inhibit the protein synthesis of bacteria. It has also shown antiviral activity against the Ebola virus, Zika virus, Rhinovirus, [21] and respiratory viral infection, [22].

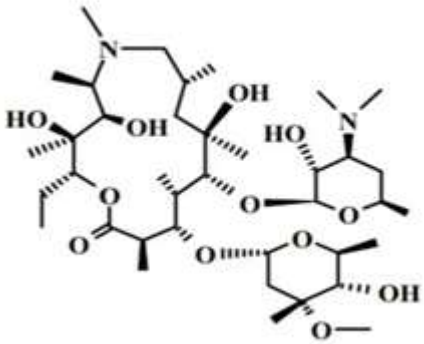

Fig. 8 The chemical structure of Azithromycin [4].

Mode of action of that drug

1) Hydroxychloroquine and chloroquine

Hydroxychloroquine and chloroquine are targeted on the lysosomes of viruses [23]. The chloroquine is accumulated in lysosomes due to pH of lysosomes is notably changed and the function of protease in lysosomes is disturbed. The degradation of proteins and glycosylation occurs. Chloroquine can affect the entry step of SARS-CoV-2 and affect the virus-cell fusion by mediated with glycosylation of ACE 2 receptor and this is attached to spike Protein. The treatment of chloroquine can be useful in the first stage of infection before COVID-19 reduces ACE 2 expression and activity. Hydroxychloroquine shows an anti-inflammatory activity on Th17 associated cytokines included (IL-6, IL-17, IL-22) present in normal persons. The chloroquine and Hydroxychloroquine also reduce the cytokines storm. In some studies shows that the main reason for the death of COVID-19 patients associated with cytokine storm. That is involved in acute respiratory distress syndrome. The various studies described the Hydroxychloroquine is effective against SARS-CoV-2 in vitro. The SARS-COV-2 and retrovirus RNA polymerase activity is inhibited by zinc. The zinc ionophores also can block the replication of these viruses [2].

2) Dexamethasone

The mode of action of dexamethasone is based upon which type of dose is used. It consists of two mechanisms like genomic and non-genomic. Low doses are used in genomic mechanisms but in the case of nongenomic mechanism, high doses are more commonly used.

Genomic mechanism

The small, lipophilic compounds, dexamethasone is freely passed across the cell membrane with the help of diffusion and then invade the cytoplasm of target cells and it begins by attached to the glucocorticoid receptor present upon the cell membrane and the formation of the complex brings to translocated the corticosteroid inside the cell, where it goes to the nucleus. It is capable to attached to the various sites of DNA. Then developing in stimulation and suppression of a wide range of gene transcription. The pro-inflammatory cytokines like interleukin IL-1, IL-2, IL-6, IL-8, TNF, IFN-gamma, VEGF, and prostaglandins inhibit their production. The five of these are associated with SARS-COV-2 severity. Simultaneously, the glucocorticoid response element is induced and activates the anti-inflammatory cytokine synthesis especially IL-10 and lipocortin-1.

Non-Genomic Mechanism

In a nongenomic mechanism, high doses are used. Dexamethasone is attached to the membrane linked GR upon the cells, like T lymphocytes developing alterations of receptor signaling and T-lymphocyte generate their immune response. The receptor such as glucocorticoid binds to integrins, then FAK (focal adhesion kinase)

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occurs. Also, high doses of dexamethasone are used that are associated with the movement of Ca+2 and Na+1 pass through the cell membrane, and the resulting action immediately reduces the inflammation [6].

3) Lopinavir / Ritonavir

The proteases play an important role in the viral life cycle. In the case of viral protease, the protease inhibitors strongly bind to the substrate site. This enzyme has the capability of post-translational proteolysis of the polyprotein and liberates the viral proteins, permit them to function properly and separately in replication/transcription and maturation. The effect inhibition shows immature virus particles are produced. Coronavirus protease consists of two in SARS-COV (a papain-like cysteine proteinase (PLpro, nsp3) and a 3C-like proteinase (3CLpro or Mpro, nsp5) and three in various distinct Coronaviruses, break the ORF-1 polypeptide and it is consequently translated. The enabled viral replication complex is formed. The substrate-binding complex is maintained by CoV 3CLpro, The broad-spectrum inhibitor triggers the region in the 3 CLpro of all CoVs. It is proposed that 3CLpro inhibiting activity of lopinavir/ritonavir show at minimum effect to anti-CoV
[24].

4) Favipiravir

Favipiravir (T705) is the purine guanine nucleotide analog [10]. It is transferred into its active form ribofuranosyl-5B-triphosphate (favipiravir-RTP) by intracellular phosphoribosylation is carried out. It is the most powerful RNA-dependent RNA polymerase inhibitor of RNA viruses. Favipiravir is integrated into the incipient viral RNA by error liable viral RdRp continue to chain termination and viral mutagenesis. The RdRp is present in several types of RNA viruses. Favipiravir facilitated a broader range of antiviral activity. Afterward, viral RNA inclusion, favipiravir-RTP acts as a mutagen. They can repair Coronaviruse machinery. The favipiravir-RTP plays a crucial role in CoV nucleotide content. In SARS-COV-2 genomes present a low cytosine about (~17.6%). In case of mutation rate is increased, the Favipiravir-RTP shows a cytopathic effect on SARS-COV-2, This is produced by the virus and decreases the count of viral RNA and infectious molecules. Favipiravir shows a high binding affinity to RdRp and their docking score is -6.925. In SARS-COV-2 present Achilles heel (RdRp) complex this complex is targeted by Favipiravir [13].

5) Ivermectin

Ivermectin shows a broad-spectrum antiviral activity in the case of various RNA Viruses [19]. It is associated withthe capability to prevent importin a/B- mediated nuclear transport due to nuclear processing of viral proteins is blocked. The Impα/β1 is required for various RNA viruses throughout the process of infection. SARS-COV-2 is an RNA virus and predicated that also showsthe same kind of mode of action. The ivermectin is acted on anti-SARS-CoV-2 in which the ivermectin is bind to the Impα/β1heterodimer and afterward the binding of Impα/β1to viral proteins is destabilized. Then prevent the viral proteins penetrate inside the nucleus. Therefore, reduces the inhibition of antiviral responses and is mediated to an effective antiviral response [16].

6) Colchicine

Colchicine is the most commonly used inhibitor of tubulin polymerization. In mechanism reported that colchicines have a strong affinity for attached to the B-tubulin subunit to stop their assembling and block the microtubule polymerization. Microtubules are the crucial component of various cellular processes that play an essential role in secreting cytokines and chemokines, cell movement, manage the shape of the cell, transfer of intracellular substances, and maintain the ion channels. Colchicine is an antimitotic substance that blocks the cell division in metaphase. It is facilitated to GTPase independent activity to help the loss of the microtubule GTP cap and restrict assembly formation. Whereas colchicine is attached to tubulin, the linear configurationαβsubunits are required for the maintain interaction between them is damaged and as decrease, the lateral contacts microtubules become disassemble. Colchicine also can change the mitochondrial membranes that depend on voltage anion channels. Colchicine also shows an effect on chemotaxis on inflammatory cells includes monocytes and neutrophils and intracellular movement of vesicles include endosomes and exosomes. The E-selection expression was also reduced. The adhesion molecule is required for the attachment of leukocytes to endothelial cells and the activity of monocytes and neutrophils to inflamed tissue are recruited. Colchicine can inhibit the neutrophil production of free radicals such as superoxide. It is

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linked to disrupting the inflammation activation and Caspase-1 activation is inhibited, Then IL-1B and IL-18 are released. The SARS-CoV-1 is linked with inflammasome activation through calcium ion movement resulting in IL-1-B are enormously produced. Direct caspase 1 activation has occurred and potassium efflux is increased [25].

7) Remdesivir

Remdesivir has a broad spectrum anti-viral activity in the case of several viruses such as Nipah, Ebola, and respiratory syncytial virus (RSV) family. The various class of coronaviruses consisting of SARS CoV and MERS CoV. Remdesivir is a nucleotide analog. Remdesivir it has occurred in form of triphosphate. The RDV-TP is utilized as a substrate for several RNA-dependent RNA polymerases (RdRp) complexes and it acts as inhibition of viral RNA synthesis by a selective mechanism of delayed chain termination occur in coronaviruses (MERS-CoV, SARS-CoV, and SARS-CoV-2) RdRp. RDV-TP it has possessed an Adenosine triphosphate (ATP) molecule and fight with nucleotide within viral RNA synthesis. The phosphodiester bond is being formed in the 3'hydroxyl group of RDV-TP with another nucleotide. But the process of viral RNA synthesis is stopped at the 3 nucleotides downstream, exactly at the i+3 position. While RDV-TP is ani-th position. This chain termination mechanism is almost similar to several viruses consisting of coronaviruses like MERS-CoV, SARS-CoV, and SARS-CoV-2. However, the exact mechanism is evasive. The major reason for chain termination is a steric clash between 1'-CN included the RDV-TP and selective residue S861 at the i+4 position. The regular chain termination at i+3 position because of the inability of RdRp to transfer a single position downstream. So finally it stops the viral RNA synthesis. Furthermore, the serine residue is maintained by all coronaviruses. The exact mechanism is not known but this is the possible description of termination of viral RNA synthesis. The Scientist demonstratesRdRp of distinct viruses and determined their kinetic parameters to assume its interaction with RDV-TP and obtained a score of 0.77 mmol half maximum concentration in case of SARS-CoV-2 [26].

8) Azithromycin

Azithromycin is acting on SARS-CoV-2 attached to respiratory cells. Its accumulation occurs intracellularly and then increases the pH and may alter the functions of the trans-Golgi network (TGN) and lysosome. The SARS-CoV-2 binding increase the pH of the Trans Golgi network may change the glycosylation of hACE2 and proteins. This macrolide also shows antiviral activity. Azithromycin brings about mimic a ganglioside of the same volume and attributes analogous chemical characteristics than GM1. The spike protein is present on the SARS-CoV-2 that takes part in the ganglioside binding site, the azithromycin can be inhibitedby SARS-CoV-2 infection by attached to the site. This action is useful for preventing the spike Protein to get reach gangliosides on the host plasma membrane that take part in SARS-CoV-2 infection. The spike Protein/CD 147 interaction or CD 147 expression is interferedwith by Azithromycin. The azithromycin increases the lysosomal pH and can alter the endocytosis process and the action of lysosomal proteases such as cathepsins or furins is essential, which may result in a difficult infusion process is occurring. The furin-like cleavage site is present on the SARS-CoV-2 spike Protein. The azithromycin reduces the activity of furins and this mechanism is useful for preventing the entry of SARS-CoV-2 inside the epithelial cells [20].

Fig.9. The life cycle of SARS-COV-2 and possible inhibition targets of antiviral drugs [10].

Contradiction

1) Hydroxychloroquine and Chloroquine

The Hydroxychloroquine and chloroquine drug is most widely used against malaria. The HCQ and CQ show various side effects such as dysentery, vomiting, nausea, and abdominalpain . This drug also shows effect on muscle fiberesi.emyopathy, other than it having effect on retina i.eretinopathy, and cardiotoxicity [27].

2) Dexamethasone

Dexamethasone is a steroid drug. Dexamethasone consistsof several adverse effects like headache, Hyperphagia, mood swings, anxiety. In some cases also observed the visual disorderswith dizziness and sometimes it can lead to arrhythmias[6]. Other side effects such as increased in weight, Acne,Sleeplessness, dizziness,wound healing,indigestion and Amensia[28].

3) Lopinavir / Ritonavir

Lopinavir / Ritonavir shows various adverse effects like nausea, vomiting, gastrointestinal intolerance, dysentery, and other major effects include cardiac abnormalities, liver toxicity, and pancreatitis. Some common effects are headache, chest pain, and Vertigo[29)

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4) Favipiravir

The side effects of Favipiravir such as dysentery, elevated transaminases, decresed count of neutrophils, and excess of uric acid in the bloodi.ehyperuricemia. Some common effects include reduces RBC production with elevated liver function parameters[29].

5) Ivermectin

The ivermectin show some common effects included is muscle aches, headache, dizziness, diarrhea, mild skin rashes, and nausea [4].

6) Colchicine

Some adverse effects are caused by colchicine. That is related to effects such as vomiting, diarrhea, nausea, and abdominal pain [17].

7) Remdesivir

Remdesivir is a antiviral drug. It acts against various infections like the Ebola virus, Coronavirus (SARS-CoV and MERS-CoV), Respiratory syncytial virus, Nipah virus, Hendra virus. The Remdesivir has various side effects include diarrhea, anemia, rash, renal impairment, hypotension, and increased hepatic enzyme [30].

8) Azithromycin

Some common effects of Azithromycin included diarrhea, nausea, stomach pain, vomiting, shortness of breath, and dizziness [4].

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