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REVIEW ON DRUG REPURPOSING DRUG USEFUL AGAINST COVID-19

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Abstract— In the world of medicine each drug has side effect at specified limit but also that drug has another use for medicinal purpose. Here also same in the COVID-19 pandemic situation we required drug that effective against COVID-19. In this review article, we collected the data of drug that has been already in market and effective against COVID-19 means repurposing of drug. In this review article mentioned the side effect of drug, dosage form, quantity of dose, biological activity and potential for use in the treatment of covid-19 disease.

Keywords—COVID-19, Drug-Repurposing, Biological Activity

I. INTRODUCTION

In this pandemic situation of covid-19, there is no identified pathological treatment available to completely treat covid-19. So, scientist agreed that to find alternative use of drug that already available in market to manage covid-19.

Repositioning drugs are new therapeutic option against covi-19 in this emergency situation. Thus, drug repositioning means in simple language another use drug of already available in market, redirecting, and re-profiling. The availability of pharmacokinetic, pharmaco-dynamics and toxicity of drug related information. One important advantage in the research effort is quickly finding an alternative drug for this deadly virus. (Serafin MB et.al (2020)

Chloroquine (CQ) and its Hydroxyl analogue Hydroxychloroquine

Chloroquine and its analogue hydroxychloroquine belongs to class of antimalarial but now a days, it is use as antiviral agent reported in many literature. It had also showed the in vitro activity to treat the COVID-19 infection. Because off increases the pH within the organelles like lysosome, endosome, golgivesical of viruses, this drug showed the antiviral activity. In one view, the mechanism of this drug is pH dependent step that is they mainly inhibit the entry of the

virus into host cell. In another view, these drugs inhibit the post-translational modifications of the virus envelope glycoproteins which are inner part of the endoplasmic vesicles as well as trans-golgi network. (Patil VM et.al (2020).

Bafilomycin A1

Bafilomycin A1 belongs to class of macrolide antibiotic. It is one of the repurposing drugs that act against the COVID-19 infection. The Mechanism of this drug is endo/lysosomal V-ATPase inhibitor which is mainly interacts in the function of the Angiotensin converting enzyme-2. Angiotensin converting enzyme-2 are mainly acting as viral receptor in SARS-CoV and SARS-CoV-2. In this case, the Bafilomycin A1 drug may stop the viral cycle at the emerging stage itself. (Pawar AY et.al (2020).

Remdesivir

Very firstly studied in Ebola virus clinical studies, it had reported that Remdesivir act as an antiviral agent. In In-vitro studies reported that it gives effective result to treat the COVID -19 infections. Remdesivir is an adenosine analogue. The mechanism of this drug is it inco-operates into viral RNA chain and this result is in premature termination. Further, more studies related to remdesivir, are anticipated in human patients of COVID-19 on the priority basis. (Singh Awadhesh et.al (2020).

Nitazoxanide

Nitazoxanide is an antiparasitic infective agent. Mainly treat the parasitic infection. At very low concentration it is effective against the various range of viruses including Human corona viruses as reported in literature. The mechanism of the nitazoxanide is selectively blocks the viral hemagglutinin intracellular trafficking and insertion of this protein into the host plasma membrane. Due to this reasons it is also use to treat COVID -19 infections. (Pawar AY et.al (2020).



Tocilizumab

It is an immunosuppressive agent. Mainly used to treat rheumatoid arthritis. Now it had tested for COVID-19. In-vivo study, the china reported it is effective against COVID-19.

Tocilizumab is one of the drug effectively decline the clinical symptoms of viral infection but the numbers of patients tested in the study were very rarer. (Pawar AY et.al (2020).

Favilavir

In 2014, Japan approved the Favilavir is an antiviral drug use to treat the influenza.it is also reported that they treat the no. of other viral infection. In these countries, currently approved for to treating the COVID-19. But yet Favilavir is not currently approved by the U.S. Food and Drug Administration (FDA). (Pawar AY et.al (2020).

Camostat mesilate

It is Inhibitors of TMPRSS2 serine protease. In a clinical trial studies, investigating that camostat mesilate treat against dyspepsia associated with non-alcoholic mild pancreatic disease, more than 90 patients received 200 mg camostat mesilate three times daily for 2 weeks and showed only mild, but no any severe adverse effects, indicating that camostat mesilate is a well-tolerated drug. (McKee Dwight L. (2020).

Favipiravir

It is an antiviral agent. The functions as an inhibiting the RNA dependent RNA polymerase. Through the compitative inhibition the efficacy of viral replication can be hugely reduced. Favipiravir was approved by National medical Products administration of china as the first anti covid-19 drug in china in March 2020 and Indian regulatory agency also approved favipiravir for mild moderate condition.

Azithromycin

It is antibacterial agent, Immune—modulatory and anti-inflammatory effectincluding effect on pro-inflammatory cytokines is observed. It was found that, those who are received adjunctive Azithromycin, they shown statistically improvement in more than 85 days survival.so it is one of the repurposing drug used to treat COVID-19 infection. It also reported that the combination drug of azithromycin and hydroxychloroquine give the synergistic effect to treat COVID-19 patients. (Pooladanda Venkatesh et.al (2020)

Lopinavir/Ritonavir

This drug are HIV proteases inhibitor. The studies reported that, the combination of these two drug was used in clinical trials against COVID-19 which showed little benefit for improving the clinical outcome. According to the WHO,

this drug may give benefits to using with other drugs such as interferon- β , oseltamivir or ribavirin etc. (Abd El-Aziz TM et.al (2020)

Sofosbuvir, Tenofovir alafenamide, Alovudine

These drugs are inhibiting the RNA dependent RNA polymerase enzyme in COVID-19 infection and then permanantly block the further infection. Due to the availability of these FDA approved drugs (Sofosbuvir, Tenofovir and AZT), they shown the hope that the drugs would be more evaluated quickly in laboratory and clinical trials for COVID-19 treatment. Some of the researcher could not offer one (or more) of them as the best RdRp inhibitor(s) to introduce to the scientific community. (Sayad B et.al(2020).

Zinc supplementation

The hypothetical study reported that, the combination of Chloroquine (CQ) and it's Hydroxyl analogue Hydroxychloroquine with zinc supplementation may be most effective to reducing morbidity and mortality rate in COVID-19 as compaired to Chloroquine (CQ) and it's Hydroxyl analogue Hydroxychloroquine monotherapy in COVID-19. Because of that CQ/HCQ in combination with zinc supplement should be considered as additional study arm for COVID-19 clinical trials. (Derwand R et.al(2020).

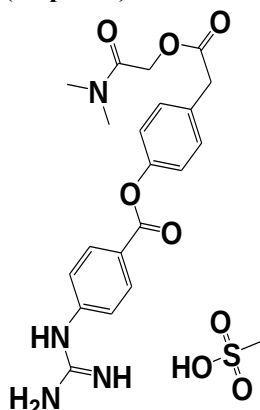
Phytochemicals and natural products targeting coronaviruses

Natural product are inhibit the viral infection as well as their replication which give the antiviral effect but the mechanism not been fully characterized. They also has function that is immunomodulators, suppressing inflammatory reaction responsible for the reducing the major morbidity and mortality rate in SARS-CoV-2 infection. Ascorbic acid (vit C), which have antioxidant properties. Many literatures reported that vit C not effective against in COVID-19 infection, but in viral respiratory infections in human beings are affected by the levels of vitamin C. In clinical studies showed that the ascorbic acid having a capacity to inhibit these process. (McKee Dwight L.(2020).

Aresenicum album 30 is a homoeopathic medicine that was recommended by Ministry of AYUSH as a prophylactic for COVID-19. There is no any evidence on whether the medicine, which is given for a broad spectrum of respiratory illnesses, holds any preventive properties for COVID -19.

II. REPURPOSING DRUGS (SERAFIN MB ET.AL (2020)

1) Drug Name with structure: Camostat Mesilate (Foipan™)



Class of Drug : Synthetic Serine protease inhibitor.

Use for : To treat chronic pancreatitis and drug inducing lung injury.

Toxicity before use : Nausea, diarrhoea, rash and pruritus.

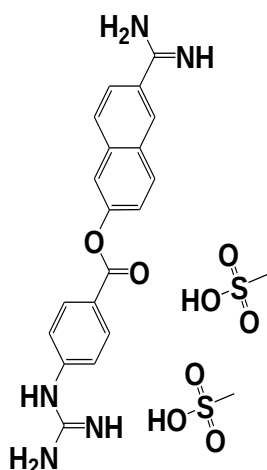
New indication in repositioning : SARS-COV2

Target : TMPRSS2

Mechanism of action : Mainly inhibit the action of serine protease TMPRSS2 preventing the priming of the viral spike for attachment to angiotensin converting enzyme2 and entry into the cell.

Dosage : 200 mg -3 times daily, for 2 weeks, per oral.

2) Drug Name with structure : Nafamostat mesilate (Buipel)



Class of Drug : Synthetic Serine protease inhibitor

Use for : Use as an anti-coagulant. Anti-pancreatitis agent

Toxicity before use : Agranulocytosis, hyperkalemia and anaphylaxis.

New indication in repositioning : MERS-CoVS, SARS-COV2

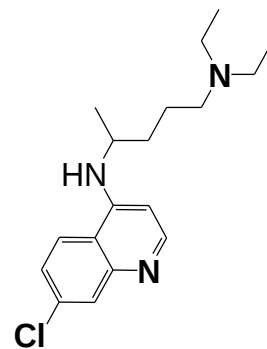
Clinical trials.gov

Target : TMPRSS2

Mechanism of action: TMPRSS2 inhibitors prevent SARS-COV2 Cell entry in vitro.(Clinical trials.gov)

Dosage : 240 mg daily, for 5 days, per oral

3) Drug Name with structure: Chloroquine phosphate (Resochin)



Class of Drug : 4-amino-quinoline

Use for : Antimalarial drug

Toxicity before use : Headache, drowsiness, visual disturbances, respiratory arrest, cardiac arrest, hypokalemia

New indication in repositioning : SARS-CoV

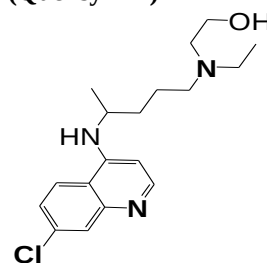
SARS-CoV-2

Target : ACE2

Mechanism of action : Because of increases the pH within the organelles like lysosome, endosome, golgi-vesical of viruses. this drug showed the antiviral activity.

Dosage : 250 mg daily until clinical convalescence, per oral.

4) Drug Name with structure : Hydroxychloroquine (Quensyl™)



Class of Drug : 4-amino-quinoline

Use for : Antimalarial drug

Toxicity before use : Headache, drowsiness, visual disturbances, respiratory arrest, cardiac arrest, hypokalemia

New indication in repositioning : SARS-CoV

SARS-CoV-2

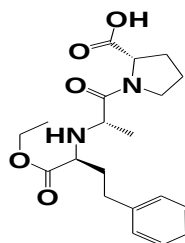
Target : ACE2



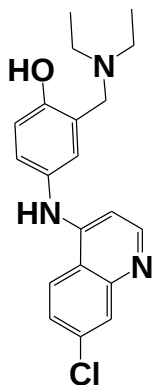
Mechanism of action : Because of increase the pH within the organelles like lysosome, endosome, golgi-vesical of viruses, this drug showed the antiviral activity.

It mainly inhibit terminal glycosylation of ACE-2, the receptor that SARS-COV and SARS-COV-2 target for cell entry.

Dosage : 400 mg loading dose twice daily at day 1, 200 mg twice daily for 4 days, or 600 mg for 6 days, or 400 mg for 5 days, peroral.



5) Drug Name with structure : Amodiaquine



Class of Drug : 4-amino-quinoline.

Use for : Antiparasitic agent.

Toxicity before use : Headache, drowsiness, visual disturbances, respiratory arrest, cardiac arrest, hypokalemia

New indication in repositioning : SARS-COV

Target : ACE2

Mechanism of action : Not determine

Dosage : Not determine

6) Drug Name with structure : Cepharanthine/selamectin/mefloquine hydrochloride (triple combination)

Class of Drug : Not determine.

Use for : cepharanthine -anti-inflammatory alkaloid
selamectin- anti-helminthic mefloquine hydrochloride-use for treatment of prophylaxis and treatment of malaria.

Toxicity before use : Not determine

New indication in repositioning : SARS-CoV-2

Target : ACE2

Mechanism of action : Inhibit the Infection of simian Vero E6 cells with pangolin coronavirus GX_P2V/2017/Guangxi (GX_P2V), whose S protein shares 92.2 % amino acid identity with that of SARS-CoV-2.

Dosage : Not determine

7) Drug Name with structure : Enalapril (Hypothesis study)

Class of Drug : ACE-2 inhibitor.

Use for : Hypertension

Toxicity before use : Cough, hypotension, headach, fatigue.

New indication in repositioning : SARS-COV-2

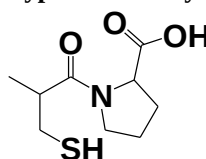
Target : ACE2

Mechanism of action : Inhibits binding between COVID-19 and human ACE-2, and reduces symptoms of severe pneumonia.

Dosage : Not determine.

8) Drug Name with structure : Captopril

Hypothesis study



Class of Drug : ACE-2 inhibitor.

Use for : Hypertension.

Toxicity before use : Emesis, decreased blood pressure.

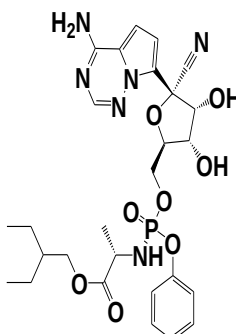
New indication in repositioning : SARS-COV-2

Target : ACE2

Mechanism of action : Inhibits binding between COVID-19 and human ACE-2, and reduces symptoms of severe pneumonia.

Dosage : Not determine.

9) Drug Name with structure : Remdesivir



Class of Drug : Adenosine triphosphate or Nucleoside analog

Use for : Clinical development for treatment of Ebola virus infection.

Toxicity before use : Not readily available



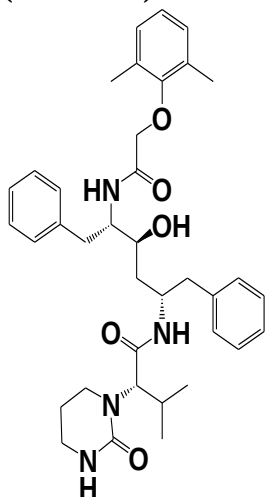
New indication in repositioning : SARS-COV-2

Target : RNA dependent RNA polymerase enzyme RdRp.

Mechanism of action : inco-operates into viral RNA chain and this result is in premature termination.

Dosage : 200 mg loading dose at day 1, 100 mg for 9–13 days, peroral or intravenous.

10) Drug Name with structure : Lopinavir/ritonavir (Kaletra™)



Class of Drug : HIV Protease inhibitor.

Use for : Antiviral drug.

Toxicity before use : Fetal cardiac shock, lactic acidosis, acute renal failure.

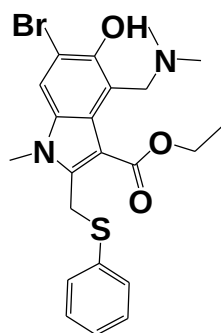
New indication in repositioning : SARS-CoV, MERS-CoV, SARS-CoV-2.

Target : Viral Proteases

Mechanism of action : Although coronavirus encoded a different enzymatic class of protease, the cysteine proteases, theoretical evidence exists that lopinavir and ritonavir also inhibit the corona viral 3CL1 pro proteases.

Dosage : 400 mg lopinavir and 100 mg ritonavir twice daily, for 14 days, per oral.

11) Drug Name with structure : Umifenovir (Arbidol™)



Class of Drug : Antiviral drug.

Use for : prophylaxis and treatment of infections with influenza A and B viruses and other respiratory viruses.

Toxicity before use : Unavailable

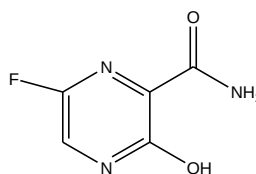
New indication in repositioning : SARS-CoV-2

Target : Membrane fusion, clathrin-mediated endocytosis.

Mechanism of action : Umifenovir prevents viral host cell entry by inhibition of membrane fusion of viral envelope and host cell cytoplasmic membrane via inhibition of clathrin-mediated endocytosis, thereby preventing virus infection.

Dosage : 400 mg three times daily, for 9 days, per oral.

Drug Name with structure : Favipiravir (Avigan™)



Class of Drug : Antiviral Drug.

Use for : It is used to treat the influenza.

Toxicity before use : Reduced body weight, vomiting and decrease the locomotor activities.

New indication in repositioning : SARS-CoV-2

Target : RdRp.

Mechanism of action : The functions as an inhibiting the RNA dependent RNA polymerase Through the competitive inhibition the efficacy of viral replication can be hugely reduced.

Dosage : 6000 mg loading dose at day 1, 2-400 mg for days 2–10, per oral

III. DESCRIPTION ABOUT SOME DRUGS THAT ARE TESTING AGAINST COVID-9

Dexamethasone is a immunosuppressive drug. Studies have that found patient with severe covid-19 have a low number of cells called T-lymphocytes in their blood. Using dexamethasone could further deplete the T-lymphocyte in their blood.

Teicoplanin is one of the drugs that belong to class of Glycopeptide antibiotic mainly used to treat the bacterial infection. This drug is used for repurposing in COVID-19 infection. The active concentration for invitro study is IC of 1.66 μ M, at very low concentration this drug active against the SARS-CoV-2. The mechanisms action of this drug is mainly Inhibited entry of COVID-19 pseudo-virus, which provides a possible strategy for prophylaxis and active against to treat COVID-19 infection. However, this requires further in vivo verification and incorporation in clinical trials. (Serafin MB et.al (2020).

Tamoxifen is used to treat Breast cancer. It is Estrogen receptor inhibitor. In vitro studies reported that the active



concentration is $EC_{50} = 92.8 \mu M$, which is required for to treat the SARS-CoV infection. COVID-19 is an infectious disease caused by SARS-CoV-2. In clinical trial, the investigators reported that according to previous research data that combination therapy of drug isotretinoin plus tamoxifen expected to provide complete protection against severe acute respiratory syndrome coronavirus, ACE2-expressing cells can act as home cells and are prone to SARS-CoV-2 infection as ACE-2 receptor facilitate cellular viral entry and replication. The dose of drug Isotretinoin plus Tamoxifen is 20 mg PO (by mouth) twice daily for 14 days.

Isotretinoin is a potential papain like proteases inhibitor which is a protein encoded by SARS-CoV-2 gene and considered one of the proteins that should be targeted in COVID-19 treatment by performing target based virtual ligand screening. The principle of investigator expects that isotretinoin can inhibit or down regulate ACE2 by direct interaction and binding with trans-membrane ACE2 suggesting its therapeutics potential in preventing the entry of COVID 19 to the host cell.

Terconazole is an Antifungal agent. It is Sterol metabolism inhibitor. Terconazole is a drug used to treat SARS-CoV infection. In-vitro studies, the active concentration is $EC_{50} = 92.8 \mu M$. Dyal et al., 2014, reported that, the mechanism of action not yet determined.

Toremifene is Estrogen receptor inhibitor. It is used to treat Breast cancer. According to literature survey, this drug is used as repurposing to treat SARS-CoV infection. In vitro studies the active concentration is $EC_{50} = 11.9 \mu M$. According to literature survey the mechanism of action not yet determined. (Serafin MB et.al (2020))

Baricitinib is an oral JAK1/JAK2 inhibitor. More than 65 countries approved for drug Baricitinib as a treatment for adult with moderately to severely active rheumatoid arthritis including warning about risk for developing serious infection, a risk that may be related to baricitinib's effect on the immune system. Given the inflammatory cascade seen in COVID -19, Baricitinib's anti-inflammatory activity has been hypothesized to have a potential beneficial effect in COVID-19 and warrants further study in patient with this infection. The receptor that SARS-CoV-2 uses to infect lung cells might be ACE2, which are prone to viral infection. (Pawar AY et.al(2020))

Thus, drug repositioning is a promising alternative for the treatment of COVID-19 disease, and a more complex investigation of the antiviral effect of these molecules against SARS- CoV-2 is encouraged.

Vaccines current status (wikipedia)

Sr no	Vaccine type	Company
1	mRNA based vaccine	Moderna
2	DNA Vaccine	Inovio and Applied DNA sciences
3	Viral vector vaccine	Vaxart, Geovax, University of Oxford, and cansino, Biologics
4	Virus like particle vaccine	Medicago, Doherty Institute
5	Recombinant Vaccines	Expree2ion, iBio, Novavax, Baylor college of medicine, university of queens-land, and Sichuan clover Biopharmaceutics, Sanofi
6	Inactivated vaccine	Sinovac biotech
7	Live attenuated vaccine	Codagenix with the serum institute of India
8	BNT 162	Pfizer and Biotech
9	Unnamed	Chinese academy of medical science
10	Covid-19/aAPC	Shenzhen Geno-immune medical institute
11	LV-SMENP-DC	Shenzhen geno-immune medical institute
12	NVX-CoV2373	Novavax

IV. CONCLUSION

The COVID-19 pandemic represents the greatest global public health crisis of this generation. There is no vaccine so, based on the all evidence, the usage of above drugs in the treatment of COVID-19 disease should be thoroughly investigated, some of them have adverse effects. The use of these drugs should be explored to treat the infection which affected by individually. All the above listed drugs can have potential to treat COVID 19 patients if sufficient In-vivo data generated about its interactions & efficacy. It is very important to follow continuously the guidelines of WHO to prevent the spread of COVID-19 until acceptable drugs and vaccines have been developed.

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