Research Into Potential Therapies Against COVID-19, With Focus On Ivermectin

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Abstract

Purpose: Ivermectin is a broad-spectrum antiparasitic and an effective drug to treat COVID-19. In this article, we looked at the effects of ivermectin on coronavirus and its patients in three ways. We have discussed and organized other previously discovered potential therapies and reviewed them in Table 2 and in the last section.

Methods: We searched for articles on MedRxiv, PubMed, Google Scholar, MEDLINE, EMBASE uses the appropriate search terms. ClinicalTrials.gov was searched for available clinical trials evaluating the effectiveness of ivermectin. We also use EU clinical trial registry data and ANZ registry data for clinical trials. Also, we performed our methods in 4 stages: Identifying studies, Selection of Studies, Collating Studies, Reporting results.

Results: Results are variable. Some studies have shown the effectiveness of ivermectin, others have not. Furthermore, some studies show that a combination of ivermectin with other drugs is useful.

Conclusion: Overall, we believe the reason ivermectin is useful is that it goes back to its origin, which is soil. Our theory and hypothesis is that if the coronavirus, created by man or by nature, can generally be treated with nature, that is, the soil. The interesting thing is that today we know that ivermectin is effective in the fight against the coronavirus. In fact, other drugs like teicoplanin, cyclosporine and rapamycin that are effective against the coronavirus have come from the soil. We hope that this article has been able to take a step in finding a corona drug, InshaAllah.

Keywords: Ivermectin, COVID-19, Potential Therapies, SARS-COV-2, COVID-19 Treatment ,Infectious Diseases

Introduction

SARS-CoV-2 was identified as an RNA virus and was first observed in patients with severe respiratory disease in Wuhan, China in late 2019 (Zhou et al., 2020). Coronaviruses consist of a lipid envelope containing a positive single stranded RNA (Phan, 2020), and SARS-CoV-2 is an enveloped β-coronavirus made up of four structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) proteins (Chen et al., 2020). The main protease (M^{pro}) plays a dominant role in processing CoV-encoded polyproteins and is recognized as an ideal antiviral target (Yang, Yang et al., 2020). SARS viruses can infect animals and in some cases viruses can infect humans (Rabi et al., 2020).

SARS-CoV-2 RNA should be identified in multiple samples as nasopharyngeal swab, oropharyngeal swab, sputum when patients were considered for clinical care and before their

isolation period [1]. It is emphasized that the coronavirus must be diagnosed and managed. COVID-19 patients should be identified and cared for at home, especially in the early stages and when they do not require hospitalization [2]. Management was not limited to people, but also to society and other issues. All three levels of analysis - macro environment, relationship, and individual - should be considered when determining families' coping strategies for their children during the COVID-19 blockade in Finland. For example, at the macro ecological level, if families are functioning social networks; at the relational level, what are the practices of the families in relation to daily life; and at the individual level, if family members have the opportunity to spend personal time [10]. Regarding food insecurity during COVID-19, lockdown restrictions in Belgium have been associated with adverse changes in most dietary habits. Government action to address malnutrition and food insecurity is necessary to protect public health from current and future pandemics [11].

Recent and ongoing outbreaks of novel coronaviruses have shed light on the question of the zoonotic origins of transmissible respiratory viruses [13]. Symptoms of COVID-19 mainly include difficulty breathing, fever, pneumonia, and lung infection (Aghagoli et al., 2020), and early symptoms include fever, dry cough, and dyspnea similar to common flu (Rothan and Byrareddy, 2020), also the fatigue, dyspnea, weakness, anxiety, and activity intolerance were the most common late symptoms [9]. The incubation period is usually around 15 days, but the reported range is 0–24 days (Bai et al., 2020). Cytokine storm is associated with severity and mortality in patients with COVID-19 (Hu et al., 2021; Kim et al., 2021). It can be argued that loss of smell and taste can predict COVID-19 disease, as it is one of the effects that the coronavirus causes in the body [4]. Also, blood type is also not associated with risk of severe disease, but patients with blood groups B and AB were more likely to be positive, as were those who are Rh^{+} positive, and blood type O was less likely to test positive [5]. Additionally, COVID-19 infection in children can present with various gastrointestinal, hepatic, and pancreatic manifestations [8].

There are many opinions about the origin of the coronavirus, whether man-made or created by nature, but bats are blamed for COVID-19 even without scientific proof. The most recent information on bats and COVID-19 indicates that bats should be considered sources of scientific research useful to human health and are not responsible for this disease [3]. When the coronavirus spread, it was initially difficult to explain the effects of the disease on children or pregnant women [12]. Regarding pregnant women, it is very important to include a group of pregnant women in clinical trials, and it is necessary to decide whether pregnant women should be included in drug efficacy studies or not [14].

Lymphopenia, low IgG2 levels, or a combination of the two can be considered to identify patients with severe COVID-19 who are at risk for MV [6]. Lymphopenia is an important feature of severe COVID-19, and a lymphocyte count below 1.5 x 109/L may be useful in predicting the severity of clinical findings [7].

Both nitazoxanide and ivermectin have been reported to have potent activity against SARS-CoV-2 in vitro [15]. Remdesivir, favipiravir, ribavirin, lopinavir-ritonavir combination, ACEIs and ARBs, ivermectin and auranofin, arbidol, tocilizumab have shown benefits in various clinical trials against COVID-19 [16]. Viral RdRP, proteases, spike protein ACE2 are among the targets of pan-coronaviruses and broad-spectrum inhibitors (Chan, 2020).

2. Methods:

2.1. Identifying studies

We searched for articles on MedRxiv, PubMed, Google Scholar, MEDLINE, EMBASE with the search terms "Ivermectin", "Combination Therapies Of Ivermectin", "Coronavirus", "SARS-CoV", "SARS-CoV-2". ClinicalTrials.gov was searched for available clinical trials evaluating the effectiveness of ivermectin. We also used data from the EU Clinical Trials Register and the ANZ Clinical Trials Register.

2.2. Selection of Studies

We reviewed and selected the relevant manuscript through reading and evaluating the title and abstracts of each study. With rigorous analysis, we omitted some irrelevant researches. Therefore, with this selection of manuscripts, we conducted a research paper.

2.3. Collating Studies

We also performed classifications to organize each datum, from manuscripts, to its relevant place to assess and evaluate.

2.4. Reporting results

Finally, with collecting and analyzing and performing our research purposes, we reported our findings. The figures were designed to improve the impact and validity of this research.

3. Results

3.1. Ivermectin

IVERMECTIN			
Properties:	Antimicrobial, Antiviral, Anticancer, Effective Against Microorganisms. (Originally Introduced As A Veterinary Drug)	**Forms Of Use:**	Tablets, Capsules, And an Oral Solution

Antiviral Effects On:	RNA, DNA Viruses	**Metabolized:**	Liver
Discovered By:	William C. Campbell, Satoshi Ōmura	**Half-life:**	24 h, Some researches declared Several Months After A Single Dose Of Ivermectin
Nobel Prize Award:	2015, Physiology Or Medicine	**Activity Of Drug In Body:**	Distributed Widely throughout the Body, due to its High Lipid Solubility, also binds strongly to plasma proteins, notably serum albumin, and is excreted in feces
FDA:	Approved	**Usual Doses:**	0.2 mg/kg to 0.4 mg/kg
First Use:	It has been in common use in veterinary medicine since 1981 for the treatment of Onchocerciasis and Filariasis. Also first used was in humans in 1987 for the treatment of Onchocerciasis	**Belongs To:**	Avermectins (Macrocyclic Lactones)
Other Use:	Onchocerciasis (River Blindness), Filariasis, Strongyloidiasis, and Scabies inhibiting the pro-liferation of cancer cells, as well as regulating glucose and cholesterol in animals	**Modern Use:**	Nanomaterial-Ivermectin composites have been proved to enhance protective efficacy and long term stability in the blood against Zika Virus in-vitro
Heavy Atoms:	62	**Aromatic Rings:**	0
H-Bond Donor (≤5)	3	**Molecular Weight (g/mol) (≤500 Da)**	875.1
Molecular Formula:	$C_{48}H_{74}O_{14}$	**Drug Classes:**	Anthelmintic Agents
ALogP	5.60	**CX LogP**	5.83
H-Bond Acceptor (≤10):	14	**Rotatable Bond count:**	8

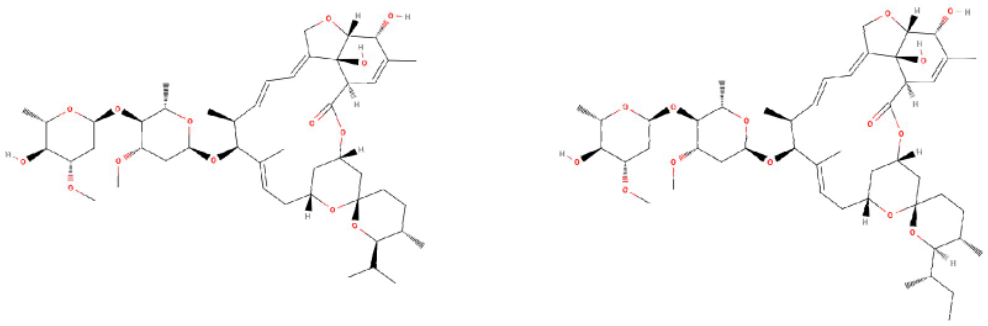
Table 1[1] [18] [19] [25] [26] [29] [30] [32] [36] [37] [39] [43] [44] [47] [50]

[1] Some Of The Data Acquired From https://pubchem.ncbi.nlm.nih.gov https://www.kegg.jp/ https://www.ebi.ac.uk/chembl/ ClinicalTrials.gov

Ivermectin is an FDA-approved broad-spectrum antiparasitic agent (Gonzalez Canga et al., 2008), and has been detected as an interaction inhibitor between the human immunodeficiency virus-1 (HIV-1) integrase protein (IN) and the importin (IMP) α/β1 heterodimer responsible for IN nuclear import (Wagstaff et al., 2011). Although the exact mechanism of action of this drug against SARS-CoV-2 is unknown (Yang et al., 2020), ivermectin suppresses SARS-CoV-2 infection in Vero-hSLAM cells (Frieman et al., 2007).

Ivermectin has also been shown to be effective against DNA viruses (Lv et al., 2018). Some drugs look for hydrophobic active patches (chloroquine, ivermectin), while others prefer hydrophilic surfaces (Remdesivir, Sofosbuvir, Eflornithine). Ivermectin inhibits the in vitro replication of some single-stranded RNA positive viruses. Caly et al. Found that the possible effects of hydroxychloroquine in combination with azithromycin against SARS-CoV-2 were widely publicized, leading in some cases to severe harm [17]. In the aquatic environment, drugs that bind to hydrophilic patches will be more stable, as their removal will lead to a reduction in structural entropy [40].

nAChRs play an important role in the pathophysiology and infection of SARS-CoV-2, and as a result, nicotine and nicotine allotropic drugs have been proposed as potential therapies for SARS -CoV-2 infection. Furthermore, ivermectin, which has been shown to inhibit the intracellular replication of SARS-CoV-2 in vitro, is a positive allogeneic modulator of α7 nAChR [41].



Ivermectin B1b

Ivermectin B1a

Figure 1[2]

[2] Figures From https://molview.org

3.2. Studies That Approve The IVM Against Covid-19

General Studies Regarding Covid-19:

Ivermectin is an effective drug to treat COVID-19 [18]. Ivermectin has been shown to have inhibitory effects on in vitro assays of viral replication [19]. Based on evidence, the use of ivermectin for both prophylaxis and treatment of COVID-19 can be proposed [20]. Remdesivir, teicoplanin, hydroxychloroquine (not in combination with azithromycin) and ivermectin could be effective antiviral drugs against SARS-CoV-2. COVID-19 patients with cytokine release syndrome can also use tocilizumab as an adjunct therapy [21]. Ivermectin could be a useful antiviral agent in several viruses, including those with positive-sense, single-stranded RNA viruses, and in the therapeutic dose range of 20 to 80 ng/mL, administration of ivermectin may be effective in the early stages of prophylaxis [22].

Studies have demonstrated the safety and efficacy of ivermectin against gnathostomiasis, scabies, strongyloidiasis, onchocerciasis and lymphatic filariasis infestations [23]. In addition, other potential drugs can be used in the treatment of COVID-19: 1) antivirals (remdesivir, ivermectin and favipiravir), 2) antimalarial (hydroxychloroquine), 3) corticosteroids (dexamethasone and methylprednisolone) and 4) CP. Further clinical trials are also needed to confirm the efficacy of Galidesivir, Sofosbuvir and Ribavirin against COVID-19 [24]. The results indicate that ivermectin has antiviral activity in vitro against SARS-CoV-2 [39]. Caly et al. stated that Ivermectin inhibited SARS-CoV-2 in vitro, using 5 μM ivermectin, for up to 48 hours. (IC_{50}; 2 μM) [45]. Like Niclosamide and Nitazoxanide that target TMEM16A (also known as anoctamin 6) and suppress its activity, Trifluoperazine, Serotonin and Ivermectin can also inhibit TMEM16F. These drugs may be candidates for COVID-19 treatment [46].

Clinical Studies Of Ivermectin:

Ivermectin accelerates recovery after ICU admission and death of inpatients (Elgazzar et al., 2020; Hashim et al., 2020; Khan et al., 2020; Niaee et al., 2020; Portmann-Baracco et al., 2020; Rajter et al., 2020; Spoorthi V, 2020). In a study dealing with COVID-19, patients were treated with a single dose of ivermectin and multiple doses of doxycycline resulted in significant improvements in symptoms and viral response (Alam et al., 2020). Ivermectin decreases mortality in critically ill patients with COVID-19 (Elgazzar et al., 2020; Hashim et al., 2020; Rajter et al., 2020). In addition, ivermectin prevents the transmission of COVID-19 disease in people exposed to infected patients (Behera et al., 2020; Bernigaud et al., 2020; Carvallo et al., 2020; Elgazzar et al., 2020; Hellwig and Maia, 2020; Shouman, 2020).

One study found that hospitalized patients who received ivermectin alongside other treatments (azithromycin and hydroxychloroquine) had lower mortality than those who did not receive ivermectin (Rajter et al., 2020). In one study, administration of ivermectin (150 μg/kg) to

hospitalized patients with COVID-19 was associated with a lower mortality rate and shorter hospital stay [42].

Ivermectin decreases morbidity and mortality from COVID-19 infection [25]. Ivermectin may be a useful model for additional therapy against coronavirus disease, leading to reduced MHV viral load and disease in mice [26]. In some African countries with large communities, the use of ivermectin is an attractive hypothesis [27]. One study observed a beneficial effect on mortality associated with the use of ivermectin in patients with COVID-19 [28]. A 5-day course of ivermectin has been shown to be safe and effective in treating adult patients with mild COVID-19 [29]. Furthermore, a three-week use of oral ivermectin is effective for the treatment of inflammatory Rosacea [30]. In one study, a single dose of IVM can reduce viral load in asymptomatic SARS-CoV-2 positive individuals. However, zinc and vitamin C were used simultaneously [31].

Ivermectin was associated with lower mortality during the treatment of patients with COVID-19, especially in patients requiring ventilator support [32]. The efficient ivermectin concentration against SARS-CoV-2 in vitro experiment by Caly et al. is 2 μM [33]. In one study, patients with non-severe COVID-19 received a single 400 mcg / kg dose of ivermectin within 72 hours and there was no difference in the number of PCR positive. However, reductions in anosmia / hyposmia and reduction in cough were observed [34].

The use of ivermectin as an anti-SARS-CoV-2 and its application in clinics can be adequately addressed to demonstrate it as a safe antiviral drug at a safe dosage [35]. The use of ivermectin early in the clinical course may reduce the rate of progression to severe disease [36]. The use of nanosuspensive mucoadhesive Ivermectin nasal spray is efficient and safe in the treatment of patients with mild COVID-19, with rapid viral clearance and reduced duration of anosmia [37]. In Colombia, chloroquine / hydroxychloroquine, lopinavir / ritonavir and ivermectin are also the only marketed antivirals available as potential treatments for COVID-19 patients [38].

Final Decision:

In general, the research examined can be criticized in several ways:

1. These articles do not mention pregnant women, those with diabetes or underlying conditions. It is not clear whether people with Asthma or type 1 and type 2 Diabetes or other types of diseases that have no medicine or treatment. Can Ivermectin be useful for them or not?

2. There is no specific standard dose in these articles that can be considered general. For example, in one article the dose used was 2 μM and in another article the effective dose was 400 mcg/kg.

3. These articles do not specify whether this drug (ivermectin) may be useful for those with severely damaged lungs or whose lungs are more severely affected by viruses.

4. Most of these articles only talked about the usefulness and effectiveness of this drug, while

there were no side effects. In fact, COVID-19 patients were tested at some point and given medication, but they were not retested after they recovered to determine whether or not the medication had side effects.

5. There was not much statistical population in these articles. For this drug to be effective, it had to be studied in many patients.

6. In these articles, there was no specific time frame for COVID-19 patient recovery. In one study, a five-day period was even helpful, and in another study a period of several weeks was effective.

7. If we want to define a drug, we must say that the drug is in fact a definitive remedy capable of curing a disease, because this drug cannot definitively cure COVID-19, so prescribing it requires caution.

3.3. Studies That Deny IVM Against Covid-19:

Compared to SOC or placebo, IVM did not reduce all-cause mortality and had no effect on AEs or major AEs and length of stay for COVID-19 patients. Moreover, IVM is not an appropriate option to treat patients with COVID-19 [43]. In a study in adults with mild COVID-19, 5-day treatment with ivermectin versus placebo, the results do not support the use of ivermectin to treat mild COVID-19 [44].

Final Decision:

In general, the research examined can be criticized in several ways:

1. It is not clear why and how, in addition to research indicating the effectiveness of this drug (Ivermectin), there are studies indicating the ineffectiveness of this drug.

2. In general, if a test is performed two or three times, it can be definitively commented. Since every experiment has an error, and by doing the same test several times and reducing the errors, we can make a good comment about it.

3. The interesting point is that in one study, this drug (Ivermectin) was reported to be useful for COVID-19 patients over a five-day period, and vice versa, in another study over the same period (5 days), it has been shown to say that this drug has no effect.

4. Showing conflicting data in research does not mean that these experiments are wrong or that the data are wrong, but that we are willing to experiment our way to find out if a drug is useful or not. Indeed, scientists and researchers prefer to follow their own path rather than the standard and common paths.

5. We do not want to criticize the research that points to the ineffectiveness of this drug, but we want to say that the results that indicate the usefulness of this drug and those that point to the

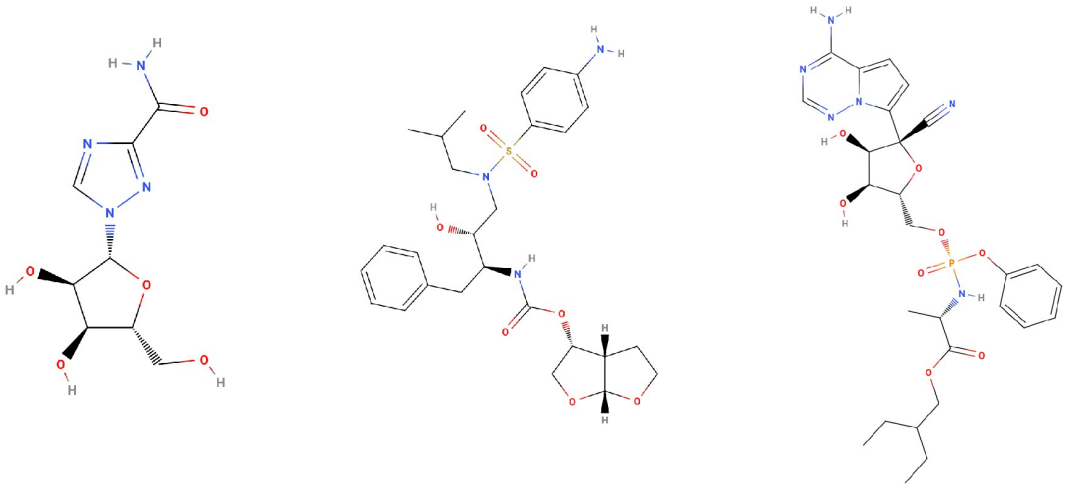
ineffectiveness of this drug achieve inconsistent results. Indicates that either the trials in both studies were not standard or the trials were flawed.

6. If the tests weren't standardized, they would have to be run again, which is unlikely because scientists try to pick the standard in their experiments, so the problem lies elsewhere, and it's the test's fault. For example, chemists repeat an experiment many times to get a valid result, but in this case, the experiments we have are not chemistry experiments because, in our case, they are people. Often we can't give this drug to our control group, which includes humans, because it has side effects, so we have to come up with another solution, and that's to expand the statistical population and the group. For example, pregnant women in a group, people with diabetes in a group, or people without the disease in a group, etc. If, for example, people suffering from asthma, diabetes or another disease, this drug is not useful and effective for them, there must be a factor that eliminates the effect of this disease, because in people who do not have the disease, that is, the drug is effective.

7. In general, these studies cannot simply be ignored and must be taken into account.

3.4. Combination Therapies Of IVM

The benefits of ivermectin or combination therapy with ivermectin against COVID-19 appear to be potentially relevant for all stages of the disease [47]. Triple therapy with ivermectin + atorvastatin + N-acetylcysteine may be an effective addition to standard of care (SOC) [48]. Furthermore, ivermectin-doxycycline combination therapy appeared to tend towards superiority over hydroxychloroquine-azithromycin combination for mild to moderate COVID-19 disease [49]. Mild to moderate COVID-19 infected patients treated with ivermectin plus doxycycline recovered earlier, were less likely to progress to more severe disease, and were more likely to be COVID-19 negative by RT-PCR on day 14 [50]. The results of one study support that the combined use of Nitazoxanide, Ribavirin and Ivermectin plus zinc supplement effectively removed SARS-COV2 from the nasopharynx [51]. In another study, combined ivermectin-azithromycin-cholecalciferol therapy for 7 days was effective in reducing the duration of symptoms and clinical progression of COVID-19 [52].



Ribavirin Darunavir Remdesivir

Figure 2[3]

Final Decision:

1. The reason why different drugs with different properties has a common effect is that there is a similar part in their chemical structure that allows all of them to bind to a single receptor.

2. Combining drugs is one of the most effective and beneficial ways to fight the disease, but the point is, it is still unclear how exactly these drugs work together to fight COVID-19. For example, if we combine two drugs (Nitazoxanide, Ribavirin) with ivermectin, of these three drugs, how effective are each of them? Or which one is more effective than the other? Or does each of them have the same percentage of efficiency?

It is even more controversial and questionable, and it is not yet known which of these three drugs will be the most effective, but the fact is that there are effectiveness and usefulness of these drugs in combination.

3.5. Other Potential Therapies Against Covid-19

In this section, we introduce other potential therapies for COVID-19:

[3] Figures from https://molview.org

Artemisinin and its derivatives present in the leaf of A. Annua are known as potential antimalarial due to their high efficiency and mainly for the downregulation of T&B cell activation, thus inhibiting the production of antibodies [53]. Another study states that corticosteroids reduce mortality in patients with severe COVID-19 and remdesivir can reduce the need for mechanical ventilation but has no effect on mortality. Interleukin-6 inhibitors (Sarilumab and Tocilizumab) and JAK inhibitors (Baricitinib and Ruxolitinib) may decrease mechanical ventilation and duration of hospitalization. But Interleukin-6 inhibitors decrease ICU length of stay and JAK inhibitors decrease mortality. Azithromycin, Hydroxychloroquine, Lopinavir-Ritonavir and Interferon beta have no benefit [54]. No form of curcumin appears to have the properties needed for a good drug candidate, but one study states that curcumin appears to have great potential for drug development [55]. Another study suggested that the anti-inflammatory effects of amantadine and memantine in vivo and clinically suggest that these effects could be of interest for the treatment of COVID-19 disease [56].

3.6. Imam Kazim Medicine[4] [57] [58] [59] [60] [61] [62] [63] [64] [65] [66] [67] [68] [69] [70]:

Imam Kazim's medicine consists of:

1. Foeniculum Vulgare 2. Mastic 3. Terminalia Chebula 4. Brown Sugar or the sugar, prepared from Saccharum Officinarum (Sugarcane)

According to the narration narrated by Hasan Ibn Bastam Ibn Sabur (Shapur), known as Ibn Bastam, one day Imam Musa Kazim fell ill and the doctors prescribed various medicines for him. Imam said, "Where are you going? Use this medicine, which is the master of medicine. Terminalia Chebula, Foeniculum Vulgar, Brown Sugar at the beginning of summer for three months, and three times a month, also at the beginning of winter for three months and three times a month, and instead of Foeniculum Vulgare uses Mastic." "So you will not get sick until you die."

Summer Ingredients: Terminalia Chebula, Foeniculum Vulgare & Brown Sugar (Spring and Summer)

Winter Ingredients: Terminalia Chebula and Mastic and Brown Sugar (Autumn and Winter)

In winter for two reasons: 1-Better conditions for some viruses 2-Weakening of the Immune System, Viral infections are more likely to increase. And in winter medicine, instead of Foeniculum Vulgare, there is Mastic that has the ability to regulate and improve the immune system.

Mastic properties: 1. Antiviral Activity 2. Antimicrobial Activity 3. Anti-Cancer activity 4. Antibacterial and Antifungal

[4] IMAM Musa al-Kazim (seventh Imam in Twelver Shia Islam)

Properties of Brown Sugar: 1. Protection of the Immune System 2. Anti-Diabetes 3. Anti-Cancer

Terminalia Chebula: 1. Antibacterial Activity 2. Antiviral Activity 3. Anti-HIV Activity 4. Anti -Cancer activity 5. Anti-Diabetic activity

Properties of Foeniculum Vulgare: 1. Anti-Cancer activity 2. Antivirus Activity 3. Antibacterial Activity

Remdesivir (GS-5734)

- Inhibits viral RNA transcription/ replication by RdRp
- Reverse Transcription Inhibitors
- Antiviral broad-spectrum drug
- Treatment of Marburg virus infections
- Activity against Filo-, pneumo-and Paramyxoviruses
- Activity against Ebola virus and Ebola disease
- Activity against epidemic and zoonotic CoVs (SARS-CoV (in vitro & in vivo) and MERS-CoV in vitro)
- Inhibits viral RdRp
- GS-441524: An antiviral nucleoside; Active metabolite of remdesivir; Form a complex with SARS-CoV-2 NSP12 RdRp; Stop the RNA replication; Terminate the RNA-chain; Bind to M^{pro}; Is not cell permeable
- RNA polymerase inhibitors
- Interrupted the viral replication (inside the host cell)
- Bind to RdRp and M^{pro} (slightly stronger interactions with RdRp than with M^{pro})
- Analogue Of Adenosine Nucleotide
- Easily cross the cellular plasma membrane
- Metabolise intracellularly
- Prodrug
- An amphiphilic molecule
- Nucleoside Analog Antiviral
- A nucleoside analog
- Inhibits the action of RNA polymerase
- Efficient against various RNA viruses also the Coronavirus MERS
- A nucleotide prodrug
- GS-5734 reduced EBOV replication in HeLa cells ($IC_{50} \approx 100$ nM)
- An IC_{50} of 340 nM in vitro
- Antiviral activity against several other viruses, including the coronavirus MERS (IC_{50} of 340 nM in vitro)
- Metabolize within cells into an alanine metabolite (GS-704277)
- Accumulated in the brain
- Targets RdRp and analogous regions of SARS-CoV-2 polymerase
- FDA approval
- EC_{50} is to be 0.77 μM in Vero E6 cells against SARS-CoV-2
- $CC_{50} > 100$μM in Vero E6 cells against SARS-CoV-2
- In combination with Baricitinib is effective
- Used clinically for the treatment of COVID-19
- An adenosine analogue
- Resistance to ExoN (Exonuclease)
- Convert to a triphosphate derivative by host enzymes
- Treat Ebola virus disease
- An RNA-dependent RNA polymerase (RdRp) inhibitor
- An experimental drug
- Inhibit viral RNA polymerase and therefore stops viral replication
- Remdesivir (RDV) therapy found no difference between 5 days versus 10 days

- Has broad-spectrum antiviral activity against several single-stranded RNA viruses
- Metabolise intracellularly to its ATP analogue
- Reduced the risk of death in severely ill patients by 67%
- Convert into its active form GS-441524 on administration
- Prodrug of an adenosine triphosphate (ATP) analog
- Some uncertainties remain on its impact on decreasing mortality
- Beneficial in improving clinical improvement of hospitalized COVID-19 patients
- Reduce viral load
- Decrease pathological processes
- Alleviated mild symptoms
- Improved pulmonary lesions in SARS-CoV-2
- Adverse effect in vivo reports
- Parent nuclei of RDV is evaluated against alpha CoV (EC_{50} = 0.78μM)
- GS-441524 (RDV's parent nucleotide) is superior and less toxic than its prodrug (also effectiveness in vivo)
- Administered intravenously
- Available as a solution and/or lyophilized powder
- Metabolize within host cells to form a pharmacologically active nucleoside triphosphate
- Intracellularly form GS-443902
- Highly metabolized
- Conversion to its active metabolite nucleoside triphosphate (NTP)
- An inhibitor of CYP3A4, OATP1B1 and OATP1B3 in vitro
- A monophosphoramidate nucleoside prodrug
- The active metabolite of Remdesivir (Remdesivir triphosphate [Remdesivir-TP] or GS-443902)
- Remdesivir-TP interfered with the nsp12 polymerase
- Showed in vitro activity on human airway epithelial cells against SARS-CoV-2
- Interfere with nsp12 polymerase
- Produce nucleoside triphosphate NTP that acts alternate substrate of RNA-chain terminator
- Effectiveness of Alphacoronavirus NL63 and several SARS/MERS-CoV coronaviruses
- A 5-day combination of interferon β-1b and Remdesivir will improve the recovery, suppress the viral load and shorten hospitalisation in patients with SARS-CoV-2 infection (NCT04647695)
- A carboxylic ester
- A single diastereomer
- Monophosphoramidate prodrug

    - H-Bond Donor (≤5): 4
    - H-Bond Acceptor (≤10): 13
    - Molecular Weight (g/mol) (≤500 Da): 602.6
    - Molecular Formula: $C_{27}H_{35}N_6O_8P$
    - Solubility: water solubility
    - Prodrug: Yes
    - Chirality: Single Stereoisomer
    - Rule Of Five: No
    - Drug type: Synthetic Small Molecule
    - ALogP:2.31
    - CX LogP:2.01
    - Aromatic Rings:3
    - Heavy Atoms:42

    - Studies involved in this research:

(Gupte et al., 2022; Cho et al., 2012; Agostini et al, 2018; Schloer et al., 2021; Gordon et al., 2020; Lo et al., 2020; Beigel et al., 2020; Wise, 2020; Goldman et al., 2020; Wang X. et al., 2020; Wang M. et al., 2020; Siegel et al., 2017; Al-Tawfiq et al., 2020; Yan and Muller, 2020; Kalil et al., 2020; Frediansyah et al., 2020; Badgujar et al., 2020; Pruijssers et al., 2020; Spinner et al., 2020 and Goldman et al., 2020; Yin et al., 2020; Shannon et al., 2020; Hanafin et al., 2021; Murphy et al., 2018; Brown et al., 2019; Amirian and Levy, 2020; Gilead, 2020; Zakiyah et al., 2021; Eastman et al., 2020; Krisanova et al. 2022; Rezagholizadeh et al., 2021; Lamb, Yvette N.

2020; Malin et al., 2020; Ferner and Aronson, 2020; Huynh et al., 2020; Nguyen et al., 2020; Zhang and Zhou, 2020)

Ribavirin

- Inhibits Viral RNA Transcription/ Replication By RdRp Reverse Transcription Inhibitors
- Broad-spectrum Antiviral
- Inhibits Viral RdRp
- RNA Polymerase Inhibitors
- Nucleoside Analogues Antivirals
- Use for HCV (Hepatitis C virus), HBV (Hepatitis C virus) and respiratory track viruses
- Metabolize in host into a guanosine analog
- Nucleoside antimetabolite drugs
- Inhibit the activity of the enzyme RdRp
- Interferes with duplication of the viral genetic material
- Mediate direct antiviral activity against a number of DNA and RNA viruses
- Increase the mutation frequency in the genomes of several RNA viruses
- RBV is a broad-spectrum antiviral prodrug
- EC_{50} of RBV as 109.50uM in vitro
- Water-Soluble
- Guanosine nucleoside analogue
- A nucleoside analogue
- Antiviral agent
- Therapy of chronic hepatitis C
- Active against many DNA and RNA viruses
- Play a crucial role in the treatment of chronic hepatitis C
- Tolerates in critically ill patients with COVID-19
- Antiviral efficacy
- Inducing mutations in RNA viral genomes
- Show promising results in treating COVID-19 patients
- Activity against RNA viruses
- May benefit COVID-19 patients
- Did not help in reducing the mortality rate in COVID-19 patients
- Inhibit IMP dehydrogenase
- Has been utilized in clinical medicine since the early 1970s
- Increase the virus clearance
- Ribavirin (1-b-D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide) was synthesized in 1970
- A study observed reduced replication of the MERS-CoV in rhesus macaques upon treatment with IFN-α2b and RBV
- Oral medication
- Should be administered with food
- A pill therapy
- FDA approved
- Treatment of head and neck cancers (Laboratory experiments)
- Abacavir decreased the level of ribavirin in the body and in the blood and in cells
- Targets a protein called "4E"

  - Molecular Weight (g/mol) (≤500 Da): 244.2
  - Solubility: water solubility
  - H-Bond Donor (≤5): 4
  - Molecular Formula: $C_8H_{12}N_4O_5$
  - H-Bond Acceptor (≤10): 7
  - Prodrug: Yes
  - Chirality: Single Stereoisomer
  - Rule Of Five: Yes

- Drug type: Synthetic Small Molecule
- ALogP: -3.01
- CX LogP:-2.77
- Aromatic Rings:1
- Heavy Atoms:17

- Studies involved in this research:

(Gish, 2006; Liu et al., 2021; Tong et al., 2020; Elia et al., 2008; Galli et al., 2018; Li et al., 2008; Briolant et al., 2004; Smee et al., 2001; Leyssen et al., 2005; Thomas et al., 2012; Wang X. et al., 2020; Loustaud-Ratti et al., 2016; Falzarano et al., 2013)

Favipiravir (T-705)

- Inhibits viral RNA transcription/ replication by RdRp
- Reverse transcription inhibitors
- Selective viral RNA-polymerase inhibitor
- Antiviral approved for treatment of novel influenza
- Inhibits viral RdRp
- Analogue of adenosine nucleotide
- Prodrug
- RNA polymerase inhibitors
- Nucleoside analog antiviral
- Mainly use for influenza virus
- Stop the replication of several other RNA viruses
- Efficacy against a broad range of influenza viruses
- A purine base analog
- A nucleoside analog
- Treating COVID-19 (in patients with mild-to-moderate illness)
- Induce viral clearance by 7 days
- Contribute to clinical improvement within 14 days
- Favipiravir triphosphate is a purine nucleoside analog
- The RdRp in RNA viruses enables antiviral activities of Favipiravir
- FPV relieve symptoms but did not improve clinical recovery rate compared with Arbidol
- An approved influenza treatment
- A pyrazinecarboxamide derivative
- Promising results in early COVID-19 clinical trials
- Favipiravir-RTP (active form; undergoes ribosylation and phosphorylation intracellularly)
- Broad-spectrum antiviral drug
- Favipiravir-RTP bind to and inhibits RdRp (prevents viral transcription and replication)
- Incorporated into the nascent viral RNA (leads to chain termination and viral mutagenesis)
- Favipiravir-RTP is ineffective against deoxyribonucleic acid
- Efficacy against the multiple types of RNA viruses over DNA viruses
- Effective against all types and sub-types of human influenza A, B and C viruses in vitro
- EC_{50} of 61.88 μM against SARS-CoV-2 in Vero E6 cells
- Safe antiviral drug for the treatment of mild-to-moderate COVID-19
- Control inflammatory mediators in COVID-19 patients
- Approved dose of FPV against influenza is associated side effects (1,600mg bid on day 1, followed by 600mg bid on days 2–5)
- Controls pneumonia progression in COVID-19 patients
- Rapid viral clearance
- Faster clinical improvement
- Efficacy against Ebola virus and Filoviruses, Flavivirus and Arenavirus, Bunyavirus
- Severe COVID-19 patients showed improvements
- Led to improved lung histology

- Shorten the viral clearance
- Reduce the SARS-CoV-2 presence in nasal secretions (during times of early symptoms of COVID-19 patients)
- Shorten clinical improvement time
- Reduce damages on radiology images
- Reduction in virus clearance time (When administered together with IFNα, compared with the protease inhibitor, Kaletra, plus IFNα)
- Improvement of lung pathology and relief of symptoms (When administered together with IFNα, compared with the protease inhibitor, Kaletra, plus IFNα)
- Increase viral clearance
- Convert to active Favipiravir ribofuranosyl-5B-triphosphate (Favipiravir-RTP) by intracellular phosphoribosylation
- Increases the rate of hyperuricemia
- Safe for short-term use but require more evaluation for long-term use
- Efficacy and safety
- Inhibit viral replication
- Prove to have significant clinical and radiological improvement (no differences on viral clearance)
- Favipiravir's effective dose against SARS-CoV-2 in vitro is much higher than Remdesivir

  - Molecular Weight (g/mol) (≤500 Da):157.104
  - solubility: water solubility
  - Molecular Formula:: $C_5H_4FN_3O_2$
  - Molecular weight (g/mol): 157.1
  - H-Bond Donor (≤5): 2
  - H-Bond Acceptor (≤10): 4
  - Prodrug:Yes
  - Chirality: Achiral Molecule
  - Rule Of Five: Yes
  - Drug type: Synthetic Small Molecule
  - ALogP:-0.58
  - CX LogP:0.25
  - Aromatic Rings:1
  - Heavy Atoms:11

    - Studies involved in this research:

(Naydenova et al., 2021; Shannon et al., 2020, Jin et al., 2013; Manabe et al., 2021; Furuta et al., 2013; Furuta et al., 2017; Chen et al., 2020; Coomes and Haghbayan, 2020; Du and Chen, 2020; Bhagat et al., 2022; Yamamura et al., 2020; Takahashi et al., 2020; Kaptein et al., 2020; AlQahtani et al., 2022; McCullough, 2020; PMDA, 2020; Shrestha et al., 2020; Tien Huy, Hirayama et al., 2022; Baranovich et al., 2013; Robson et al., 2020; Fu et al., 2020; Ivashchenko et al., 2021; Chen et al., 2020; Patil et al., 2021; Wang et al., 2020; Cai et al., 2020; Pilkington et al., 2020; Wang M. et al., 2020)

Chloroquine

- Increases endosomal pH
- Interferes with ACE2 glycosylation
- Prevent virus attachment
- Antimalarial
- Inhibit action of heme polymerase
- Inhibit terminal glycosylation of ACE2 (SARS-COV-2)
- Broad-spectrum antiviral
- Used to prevent and to treat autoimmune diseases (also amebiasis, rheumatoid arthritis, and lupus erythematosus)
- Acidification in endosomes and lysosomes
- Suppress the PICLAM

- Prevents the biosynthesis of sialic acid
- Inhibition of pH dependent endocytosis
- Inhibit viral binding to its cell surface receptor
- MAPK inhibitor
- Autophagy inhibitor
- Inhibitor of pro-inflammatory cytokines
- Inhibit the action of heme polymerase
- High selectivity indices
- An aminoquinoline
- An antirheumatic drug
- A dermatologic drug
- An autophagy inhibitor
- Effective against COVID-19 in vitro
- An anticoronaviral agent
- Originated from Quinine
- Reduced the recovery time (in COVID-19 patients)
- Improve physiological conditions (in COVID-19 patients)
- Result of HCQ in clinic showed better than CQ (in protective effect with low dosage)
- An antimalarial drug
- First drug used for malaria
- An alkaloid
- Reduced the number of Zika-infected cells in vitro
- Inhibit virus production and cell death promoted by Zika infection without cytotoxic effects
- CQ and HCQ both belong to the 4-Aminoquinoline chemical class
- CQ (Dose 500mg bid, 15days) may work more efficiently than LPV/RTV
- Inhibits the infection and transmission of SARS-CoV via
- Increase endosomal pH
- Interfere with the glycosylation of cellular receptors of SARS-CoV
- Using CQ and HCQ against COVID-19
- CQ clinic history could be traced back to 1820
- Candidate for treating EBOV
- Replication of EBOV was impaired by CQ in vitro
- Blocks the production of proinflammatory cytokines
- Possible therapy for shortening the duration of COVID-19
- High dose CQ was associated with high mortality
- Blocks COVID-19 infected Vero E6 cells in vitro
- Inhibits the CHIKV infection in Vero cells
- Broad-spectrum activity against Coronavirus
- Block viral infection

  - Molecular Weight (g/mol) (≤500 Da): 319.9
  - solubility: very slightly soluble in water but soluble in DIL ether
  - Molecular Formula: $C_{18}H_{26}ClN_3$
  - H-Bond Donor (≤5): 1
  - H-Bond Acceptor (≤10): 3
  - Prodrug:No
  - Chirality: Racemic Mixture
  - Rule Of Five: Yes
  - Drug type: Synthetic Small Molecule
  - ALogP:4.81
  - CX LogP:3.93
  - Aromatic Rings:2
  - Heavy Atoms:22

  - Studies involved in this research:

(Ross, 1918; Wang et al., 2020; Xiao et al., 2020; Organization, 1990; Al-Bari, 2020; Colson et al, 2020; Khan et al., 2010; Delvecchio et al., 2016; Borba et al., 2020; Chatre et al., 2018; Yakoub AdenAbdi OE et al., 1995; Ross, 1918; Vincent et al., 2005; Carrière et al., 2020; Beigel et al., 2020; Colson et al., 2020; Gao et al., 2020; Coomes & Haghbayan, 2020; Li & De Clercq, 2020; Xiao et al., 2020; Paton et al., 2011; Devaux et al., 2020; Gautret et al., 2020; Dowall et al., 2015; Huang M. et al., 2020; Samanidou et al., 2005)

Hydroxychloroquine

- Increases endosomal pH
- Interferes with ACE2 glycosylation
- Prevent virus attachment
- CQ or HCQ does not improve clinical results in COVID-19
- Anti-malarial
- Increase mortality in COVID patients (combination of HCQ and AZM)
- Early viral clearance (combination of HCQ and AZM)
- MAPK inhibitor
- Inhibit SARS-CoV-2 replication
- Aminoquinoline
- No efficacy of HCQ against COVID-19
- Autophagy inhibitor
- Inhibit the endocytosis-mediated viral entry into host cells
- A racemic mixture consisting of an R and S enantiomer
- Inhibitor of pro-inflammatory cytokines
- N-ethyl groups is hydroxylated at position 2
- An antimalarial
- Anti-inflammatory
- Acts against erythrocytic forms of malarial parasites
- Mechanism of action against coronavirus: modification of viral S glycoprotein and post-translational modification of the ACE2 receptor glycoprotein
- Derivative of chloroquine
- Inhibit terminal glycosylation of ACE2 (SARS-COV-2)
- An anticoronaviral agent
- An antirheumatic drug
- A dermatologic drug
- Has a long duration of action
- May lead to severe hypoglycemia
- Better COVID-19 viral elimination (combination of Azithromycin and Hydroxychloroquine)
- In vitro activity with a lower EC_{50} for SARS-CoV-2 (HCQ: 6.14μM and CQ: 23.90μM)
- Acidification in endosomes and lysosomes
- Reduce mortality in COVID-19 patients (combination of Azithromycin and Hydroxychloroquine)
- Greater changes in QTc in COVID-19 patients (treatment of AZM and HCQ)
- Treating COVID-19 patients with CQ/HCQ did not reduce mortality
- CQ/HCQ alone or in combination with AZM increased the duration of hospital stay
- Virological cure rate and that on days 4, 10, or 14 were not affected by receiving HCQ
- Doesn't have benefit in terms of virological cure as well (Adding AZM to HCQ/CQ)
- Avoid high doses use of CQ/HCQ (either alone or in combination with other antivirals) (lead to tissue injury in the liver, retina, skeletal, and cardiac muscle cells due to their lysosomal affinity)
- Hydroxychloroquine is ineffective in COVID-19 and has serious side effects
- Chloroquine phosphate: inhibit SARS-CoV-2 infection in vitro; shorten the time of viral clearance; improve clinical symptoms in patients with COVID-19
- HCQ treated patients did not either benefit or suffer in terms of intubation or mortality also neither HCQ nor AZM separately or together could decrease the mortality of COVID-19 patients (Reports from United States)
- Treatment of rheumatic diseases
- Inhibitory effects on a variety of Coronaviruses, including SARS-CoV-2
- Immunomodulatory effects
- Effective treatment in pregnant women against the SARS-CoV-2 infection and associated with decreased

mortality (combination of Azithromycin and Hydroxychloroquine)

- FDA issued and revoked CQ and HCQ against COVID-19

  - Molecular Weight (g/mol) (≤500 Da): 335.87
  - solubility: water solubility
  - Drug likeliness (based on Lipinski's Rule of Five): Yes
  - Molecular Formula: $C_{18}H_{26}ClN_3O$
  - H-Bond Donor (≤5): 2
  - H-Bond Acceptor (≤10): 4
  - Prodrug: No
  - Chirality: Racemic Mixture
  - Rule Of Five: Yes
  - Drug type: Synthetic Small Molecule
  - ALogP:3.78
  - CX LogP: 2.89
  - Aromatic Rings:2
  - Heavy Atoms:23

  - Studies involved in this research:

(Shalimar et al., 2020; Fiolet et al., 2020; Gautret et al., 2020; Liu et al., 2020; Samanidou et al., 2005; Mercuro et al., 2020; Li et al., 2003; Vincent et al., 2005; Bonny et al., 2020; Arshad et al., 2020; Yao X. et al., 2020; Satarker et al., 2020; Cohen, 2020; Almaghraby et al., 2020; Huang et al., 2020; Teixeira et al., 2002; Malviya, 2020; Horby et al., 2020; Acharya and Sayed, 2020; Geleris et al., 2020; National Institutes of Health, 2020; Rosenberg et al., 2020; Geleris et al., 2020; Rolain et al., 2007; Wang M. et al., 2020; Persoons et al., 2021; Sisti et al., 2020; Chandra Jha et al., 2021; FDA, 2020)

Umifenovir (Arbidol)

- Block ACE2
- Prevent virus attachment
- Fusion inhibitors
- JAK kinase inhibitor
- Arbidol (UFV) is used as a treatment and prevention measure against influenza virus
- Non-nucleoside HA inhibitor Antivirus
- Interact preferentially with aromatic amino acids
- Treatment and prophylaxis of other respiratory infections
- Was not beneficial to improve the condition of the patient (viral clearance)
- Membrane haemagglutinin fusion inhibitor in influenza viruses
- Arbidol + LPV/RTV were associated with many adverse events
- Antiviral potent broad-spectrum
- Treat hepatitis C virus
- The EC_{50} and CC_{50} were 4.11 and 31.79μM
- Neutralized the SARS-CoV-2
- Targets S protein / ACE interaction
- Anti-inflammatory activity
- Inhibit one (or several) stage(s) of the viral life cycle
- Direct-acting virucidal activity
- Broad-spectrum of activity (both enveloped and non-enveloped RNA and DNA viruses)
- Indole derivative
- Anti-inflammatory
- An orally bioavailable
- Inhibit the fusion of the viral envelope with host cell membrane
- Prevent viral infection and replication.
- Interfere in virus binding to host cells
- Block the entry of virus into host cells

- An indolyl carboxylic acid
- Efficacious, safe and well-tolerated (at dosage of 800mg BID, maximum 14 days)
- Has been used in the treatments of influenza viruses
- Enhanced its efficacy in vivo
- Umifenovir (trade name: Arbidol)
- Efficacy for Mild-asymptomatic patients
- A fusion inhibitor
- Broad-spectrum antiviral
- Inhibits COVID-19 infection
- ARB (Arbidol) prevents contact and penetration of virus to host cells
- Affects multiple stages of the virus life cycle
- Improved the discharging rate and decreased the mortality rate
- Avoid the fusion of the virus lipid shell to the cell membrane
- Inhibit viral attachment
- Effective against SARS-CoV-2 in vitro
- Released of SARS-CoV-2 from intracellular vesicles
- Not associated with improved outcomes
- Inhibits viral fusion with host cells
- Direct antiviral and host-targeting action
- Interacts with virus protein or lipid components
- Hinder different stages of the viral life cycle
- Inhibits viral entry by binding to envelope protein
- Inhibits various isolates of zika virus in multiple cell lines
- Prevent and treat influenza
- Not effective in reducing the SARS-CoV-2 elimination (infected patient)
- Not effective in reducing hospital length of stay of hospitalized patients
- Not effective in reducing detection in diagnostic tests
- Efficacy against a number of viruses in vitro and in vivo
- Bind to the spike-ACE2 interface to block attachment (Arbidol derivatives)
- COVID-19 patients provided with UFV along with LPV/RTV showed better outcomes compared to patients who received LPV/RTV only
- Structural similarities between the drug-binding regions of influenza virus HA and SARS-CoV-2 S glycoprotein (therefore, arbidol may target the latter and impede its trimerization to exert antiviral effects)
- Inhibit influenza virus fusion
- Inhibit SARS-CoV-2 infection in vitro
- Block SARS-CoV-2 entry (preventing attachment and release from intracellular vesicles)

  - Molecular Weight (g/mol): 477.4145(≤500 Da)
  - solubility: water solubility
  - Molecular Formula: $C_{22}H_{25}BrN_2O_3S$
  - H-Bond Donor (≤5): 1
  - H-Bond Acceptor (≤10): 5
  - Prodrug: No
  - Chirality: Achiral Molecule
  - Rule Of Five: No
  - Drug type: Synthetic Small Molecule
  - ALogP:5.18
  - CX LogP:3.75
  - Aromatic Rings:3
  - Heavy Atoms:29

  - Studies involved in this research:

(Wen et al., 2020; Tripathi et al., 2020; Lian et al., 2020; Blaising et al., 2014; Herod et al., 2019; Deng et al., 2020; Tripathi et al., 2020; Ramachandran, Kundu et al., 2021; Blaising et al., 2014; Vankadari, 2020; Teissier et al., 2011; Kadam and Wilson, 2017; Hulseberg et al., 2019; Nojomi et al., 2020; Wang et al., 2020; Zhu Z. et al.,

2020; Wang X. et al., 2020; Huang et al., 2021; Choudhary and Silakari, 2020; Nojomi et al., 2020; Huang D. et al., 2020; Kadam and Wilson, 2017; Leneva et al., 2016; Pécheur et al., 2016; Ma et al., 2019; Fink et al., 2018; Vankadari, 2020; Wang X. et al., 2020; Zhu et al., 2020)

Lopinavir

- Protease inhibitors
- Inhibit the activity of an enzyme critical for the HIV viral lifecycle
- An antiretroviral protease inhibitor
- Therapy and prevention of HIV (human immunodeficiency virus) infection and the AIDS (acquired immunodeficiency syndrome) (in combination with ritonavir)
- A dicarboxylic acid diamide
- Used to human immunodeficiency virus (HIV)
- Use for prevention after a needlestick injury
- 3-chymotrypsin-like protease ($3CL^{pro}$) and papain-like protease (PL^{pro})
- Previous use in HIV
- Acts on the viral 3-chymotrypsin-like protease ($3CL^{pro}$)
- HIV-1 protease inhibitor
- Arbidol monotherapy was better against COVID-19 (superior to LPV/RTV)
- Increases plasma half-life (with Ritonavir)
- Adverse gastrointestinal effects observed in patients treated with LPV/RTV (diarrhea, nausea and vomiting)
- Reduce viral shedding (LPV/RTV treatment is initiated within 10 days of symptom onset)
- Inhibits polyprotein proteolysis mediated by M^{pro} / PL^{pro}
- Block viral cellular entry
- Lopinavir (LPV) is an established antiretroviral (ARV) agent
- Use as part of antiretroviral therapy (ART) in pediatric populations
- HIV protease inhibitor
- An anticoronaviral agent
- An antiviral drug
- A member of amphetamines
- Lopinavir/Ritonavir (LPV/r) is recommended by (WHO) as first-line treatment for HIV-infected infants and young children
- In vitro LPV effectiveness against SARS-CoV at 4μg/ml
- Kaletra is a FDA-approved
- Inhibit Gag-Pol polyprotein division
- LPV/RTV treatment improve physiological condition without adverse events
- Inhibitor of SARS-CoV main protease (critical for replication)
- FPV has better action and fewer adverse effects than LPV/RTV
- Inhibit Gag-Pol polyprotein division
- Lopinavir–Ritonavir was not associated with reductions in 28-day mortality, duration of hospital stay, or risk of progressing to invasive mechanical ventilation or death (In patients with COVID-19)
- Treatment for COVID-19 (in vitro) (Lopinavir–Ritonavir)
- Reduce disease symptoms and virus shedding (triple therapy: RBV considered was 400mg bid along with 400mg/100mg of LPV/RTV + IFN-α for 14 days)
- The mortality was higher (33%) in COVID-19 patients treated with RBV than that of Sofosbuvir/Daclatasvir
- Arbidol + LPV/RTV were associated with many adverse events
- In vitro inhibitory activity against SARS-CoV and SARS-CoV-2 and MERS coronavirus
- Inhibit $3CL^{pro}$

  - Molecular Formula: $C_{37}H_{48}N_4O_5$
  - Molecular weight (g/mol) (≤500 Da): 628.8
  - H-Bond Donor (≤5): 4
  - H-Bond Acceptor (≤10): 5
  - Prodrug: No
  - Chirality: Single Stereoisomer
  - Rule Of Five: No

- Drug type:Synthetic Small Molecule
- ALogP: 4.33
- CX LogP:4.69
- Aromatic Rings:3
- Heavy Atoms:46

- Studies involved in this research:

(Horby et al., 2020; Mangum and Graham, 2001; Rock et al., 2014; Zhu et al., 2020; Deng et al., 2020; Cai et al., 2020; Yan et al., 2020; Sisay, 2020; Wen et al., 2020; Huang Y.-Q. et al., 2020; Liu W. et al., 2020; Vecchio et al., 2020; Mangum and Graham, 2001; Horby et al., 2020; Chu et al., 2004; Eslami et al., 2020; Cvetkovic and Goa, 2003; Wu et al., 2004; Uzunova et al., 2020; Ye et al., 2020; Lê et al., 2020; Chandwani and Shuter, 2008; Capparelli et al., 2018; Hung et al., 2020)

Ritonavir

- Antiviral generally
- Used to HIV (But is no longer used for its activity against HIV. Instead, ritonavir (given at low doses) is currently used as a pharmacokinetic enhancer to boost the activity of other HIV medicines)
- Use for prevention after a needlestick injury
- Inhibits polyprotein proteolysis mediated by M^{pro} / PL^{pro}
- 3-chymotrypsin-like protease ($3CL^{pro}$)
- Papain-like protease (PL^{pro})
- Previous use in HIV
- The design is based on the symmetry of the protease
- Protease inhibitors
- Appear to be a safe
- Effective antiretroviral agent
- Block viral cellular entry
- Ritonavir (brand name: Norvir)
- Approved by FDA
- Use in combination with other HIV medicines

- Ritonavir (RTV) is an L-valine derivative
- When ritonavir is used as a pharmacokinetic enhancer, it does not work as an HIV medicine and does not treat HIV
- Bind to the protease active site (inhibits the activity of the enzyme)
- A potent inhibitor in vitro of HIV-1(human immunodeficiency virus type 1) protease
- HIV protease inhibitors (Ritonavir and Lopinavir)
- Inhibits aspartic protease (prevents processing of the Gag-Pol polyprotein precursor)
- LPV/RTV may decrease mortality
- Lopinavir/Ritonavir was less efficient than Favipiravir in terms of viral clearance and disease progression, with more adverse events recorded
- No benefit of LPV/RTV (Dose: 400mg/100mg bid, 14 days) treatment
- No benefit for the primary endpoint beyond standard care but shows benefit for some secondary endpoints (Lopinavir/Ritonavir) (patients with severe COVID-19)
- Inhibits M^{pro} of SARS-CoV in vitro
- Successful treatment of non-severe COVID-19 pneumonia patients with LPV/RTV
- LPV/RTV treatment did not decrease the duration of viral shedding in infected patients
- No benefit in the time to clinical improvement was observed in the Lopinavir/Ritonavir
- Little improvement of clinical outcome (Lopinavir/Ritonavir combination in patients with mild or moderate COVID-19) (NCT04252885)
- Did not considerably decrease mortality and clinical symptoms (Lopinavir/Ritonavir) (patients with COVID-19)
- Treat COVID-19 targeting M^{pro} (Lopinavir/Ritonavir)

  - Molecular Formula: $C_{37}H_{48}N_6O_5S_2$
  - Molecular weight (g/mol) (≤500 Da): 720.9
  - H-Bond Donor (≤5): 4
  - H-Bond Acceptor (≤10): 9
  - Prodrug: No
  - Chirality: Single Stereoisomer
  - Rule Of Five: No
  - Drug type: Synthetic Small Molecule
  - ALogP:5.91
  - CX LogP:5.22
  - Aromatic Rings:4
  - Heavy Atoms:50

    - Studies involved in this research:

(Kim, J., Jung, J., Kim, T.H. et al., 2021; Huang Y.-Q. et al., 2020; Verdugo-Paiva et al., 2020; Markowitz et al., 1995; Karolyi et al., 2020; Horby et al., 2020; Wu et al., 2004; Uzunova et al., 2020; Baden and Rubin, 2020; Liu and Wang, 2020; Wang, 2020; Cai et al., 2020; Walmsley et al., 2002; Ma et al., 2020; Nutho et al., 2020; Yao T. et al., 2020; Beyls et al., 2020; Wada et al., 2020; Cao et al., 2020; Cheng et al., 2020; Cvetkovic and Goa, 2003; Chandwani and Shuter, 2008; Pan et al., 2021; Stower et al., 2020; Li et al., 2020; Chan et al., 2003, 2015)

Darunavir

- Protease inhibitors
- An antiretroviral protease inhibitor
- EC_{50} > 100 μM
- Not in vitro antiviral activity against SARS-CoV-2
- Darunavir (DRV) and LPV are both HIV-1 protease inhibitors that share a similar mechanism for inhibiting HIV replication
- Inhibits polyprotein proteolysis mediated by M^{pro} / PL^{pro}
- Inhibit $3CL^{pro}$
- Antiretroviral drug
- Used to treat and prevent HIV/AIDS

- Use as prevention after a needlestick injury
- Prevents COVID-19 protein synthesis (Darunavir Ethanolate)
- In patients with COVID-19, early treatment with Lopinavir-Ritonavir was associated with faster time to reach the primary composite endpoint of clinical improvement and/or virological clearance than treatment with Darunavir-Cobicistat
- Approved by FDA
- Darunavir (brand name: Prezista)
- Use in combination with a boosting agent (a pharmacokinetic enhancer) (ritonavir cobicistat and other HIV medicines)
- HIV-1 protease nonpeptidic inhibitor
- Oral administration
- Inhibit the dimerization and catalytic activity of HIV-1 protease
- Selectively targets and binds to the active site of HIV-1 protease
- An inhibitor of (HIV) protease
- Prevent HIV viral replication
- Reduced viral load and increased CD4 cell counts, reduced the morbidity and mortality of HIV infection (ritonavir in combination)

  - Molecular Weight (g/mol) (≤500 Da): 547.7
  - Molecular Formula: $C_{27}H_{37}N_3O_7S$
  - H-Bond Donor (≤5): 3
  - H-Bond Acceptor (≤10): 9
  - Prodrug: No
  - Chirality: Single Stereoisomer
  - Rule Of Five: No
  - Drug type: Synthetic Small Molecule
  - ALogP:2.38
  - CX LogP:2.82
  - Aromatic Rings:2
  - Heavy Atoms:38

  - Studies involved in this research:

(Elmekaty et al., 2021; Chavda et al., 2021; Lu et al., 2020; Meyer et al., 2020)

Tocilizumab

- Bind to IL-6 receptors
- Antibiotic (Gram-positive bacteria)
- Inhibit IL-6 mediated inflammatory pathways
- Immunosuppressive drug
- Prevents IL-6 receptor activation
- A lower mechanical ventilation requirement among COVID-19 patients
- A lower risk of mortality among COVID-19 patients
- Inhibits IL-6 signaling
- DEX (Dexamethasone) and TCZ (Tocilizumab) reduce the occurrence of death and ventilatory support (In moderate-to-severe COVID-19 pneumonia)
- Potential therapy for COVID-19 patients (having a cytokine storm)
- Efficacy for the treatment of Rheumatoid Arthritis (RA)
- Treatment of systematic juvenileidiopathic arthritis
- A monoclonal antibody against IL-6 receptor (IL6-R)
- An immunosuppressive drug
- IL-6 antibody
- Use as prophylaxis
- Treatment of methicillin-resistant Staphylococcus aurenus and Enterococcus faecalis
- Against the Interleukin-6 (IL-6)

- Significant clinical improvement
    - Studies involved in this research:

(Hermine et al., 2022; Klopfenstein et al., 2020; Toniati et al., 2020; Zou et al., 2021; Scott, 2017; Shimizu et al., 2021)

Sarilumab

- Binds to IL-6 receptors
- Inhibit IL-6 mediated inflammatory pathways
- Treatment for severe SARS-CoV-2 pneumonia (IL-6R inhibition)
- Monoclonal antibodies to IL-6R
- Prevents IL-6 receptor activation
- A safe drug
- Inhibits IL-6 signaling
- Potential treatments for severe COVID-19
- Approved for use in Rheumatoid Arthritis
- Good clinical outcomes in patients with COVID-19
- Significant improvement in health condition (in patients with severe COVID-19 in the ICU)
    - Studies involved in this research:

(Gremese et al., 2020; Shah et al., 2021; Branch-Elliman et al., 2022)

Baricitinib

- Fusion inhibitors
- JAK1/JAK2 inhibitor (JAK kinases: intracellular enzymes; involved in cytokine signaling, inflammation, immune function and hematopoiesis)
- Selective Janus kinase 1/2 inhibitor
- High binding affinity for AAK1 and GAK
- Anti-inflammatory
- An ATP-competitive kinase inhibitor
- Immunomodulating
- Anti-inflammatory
- Antineoplastic
- An orally bioavailable inhibitor
- Inhibition of the JAK-signal transducers and activators of transcription (STAT) signaling pathway
- Reduce proliferation of JAK1/2-expressing tumor cells
- Preventing damage to the lungs and other organs
- Induce apoptosis
- Potential therapeutic against SARS-CoV-2
- Block SARS-CoV-2 entry into cells for replication
- Baricitinib plus Remdesivir was better in decreasing recovery time (superior to Remdesivir alone)
- Inhibits the pro-inflammatory signals of various cytokines (such as IL-6, IL-12, and IL-23)
- A pyrrolopyrimidine
- Reduced mortality (Baricitinib with Dexamethasone) (in hospitalised adults with COVID-19)
    - Molecular Weight (g/mol) (≤500 Da): 371.4
    - Molecular formula: $C_{16}H_{17}N_7O_2S$
    - H-Bond Donor (≤5): 1
    - H-Bond Acceptor (≤10): 7
    - Prodrug: No
    - Chirality: Achiral Molecule

- Rule Of Five: Yes
- Drug type: Synthetic Small Molecule
- ALogP:1.10
- CX LogP:-0.19
- Aromatic Rings:3
- Heavy Atoms:26

- Studies involved in this research:

(Zhang X. et al., 2020; Marconi et al., 2021; Kalil et al., 2021; Keystone et al., 2015; Lu et al., 2020)

Camostat Mesylate

- Fusion inhibitors
- Camostat Mesylate and Nafamostat Mesylate are structurally similar guanidinobenzoic acid derivatives
- Camostat Mesylate and Nafamostat Mesylate are cellular protease inhibitors
- Suppress the activities of kallikrein, trypsin, thrombin, and TMPRSS2 (Camostat Mesylate and Nafamostat Mesylate)
- Inhibits TMPRSS2 (transmembrane protease, serine 2)
- Protease inhibitor
- Bind to all three pockets of TMPRSS2 (S1, catalytic triad domain, and hydrophobic patch)
- Severity of coronavirus disease 2019 decreased
- Anti-SARS-CoV-2 activity
- inhibit SARS-CoV-2 infection
- Prevents viral cell entry
- CM (Camostat Mesylate) block the spread of SARS-CoV (expected to show similar effect in MERS-CoV)
- Hydrolyzed in vivo to its active metabolite 4-(4-guanidinobenzoyloxy) phenylacetic acid
- Block the virus-activating host cell protease TMPRSS2
- Camostat Mesylate suppressed SARS-CoV-2 activity in vitro (also Nafamostat Mesylate)
- Approved for human use in Japan
- Camostat in Japan known as “Foipan” and certified for patients with chronic pancreatitis
- Camostat Mesylate is the mesylate salt form of camostat
- An orally bioavailable
- Antifibrotic
- Synthetic serine protease inhibitor
- Anti-inflammatory
- Antiviral activities

- Molecular Weight (g/mol) (≤500 Da): 494.5
- Molecular formula: $C_{21}H_{26}N_4O_8S$
- H-Bond Donor (≤5): 3
- H-Bond Acceptor (≤10): 9
- Prodrug: No
- Chirality: Achiral Molecule
- Rule Of Five: Yes
- Drug type: Synthetic Small Molecule
- ALogP:1.39
- CX LogP:1.51
- Aromatic Rings:2
- Heavy Atoms:29

- Studies involved in this research:

(Bittmann et al., 2020; Wang M. et al., 2020; Breining et al., 2021; Gunst et al., 2021; Uno et al., 2020; Hoffmann et al., 2021; Hofmann-Winkler et al., 2020)

Atazanavir

- Protease inhibitors
- Potential repurposing drug to COVID-19
- Reduce the SARS-CoV-2-induced IL-6 levels
- ATZ/RTV is better tolerated in comparison with LPV/RTV
- ATZ/RTV did not show more effectiveness in comparison with LPV/RTV in clinical outcomes of COVID-19
- Block M^{pro} activity
- ATV/RTV also impaired virus-induced enhancement of interleukin 6 (IL-6)
- Atazanavir (brand name: Reyataz)
- Approved by FDA
- Treatment of HIV infection
- Atazanavir (ATV)
- Activity against HIV-1
- Bind to the protease active site
- An azapeptide HIV-1 protease inhibitor (PI)
- Inhibit the activity of the enzyme
- Docks in the active site of SARS-CoV-2 M^{pro}

    - Molecular Weight (g/mol) (≤500 Da): 704.9
    - Molecular formula: $C_{38}H_{52}N_6O_7$
    - H-Bond Donor (≤5): 5
    - H-Bond Acceptor (≤10): 9
    - Prodrug: No
    - Chirality: Single Stereoisomer
    - Rule Of Five: No
    - Drug type: Synthetic Small Molecule
    - ALogP:4.21
    - CX LogP:4.54
    - Aromatic Rings:3
    - Heavy Atoms:51

    - Studies involved in this research:

(Augusto Chaves, Moreno L. Souza et al., 202; Kasgari et al., 2021; Moreno L. Souza et al., 2022)

Amantadine (M2 ion-channel protein blockers)

- Neuraminidase Inhibitors
- Affects the known SARS-CoV-2 mutations
- Block the ion channel activity of ORF10
- Reduce risk of COVID-19 infection
- Antiviral properties
- Used to treat influenza A in 1963
- Prophylactic treatment in 1976 against the influenza virus A
- Combine with L-DOPA
- Dopaminergic activity
- Interfere with the function of the transmembrane domain of the viral M2 protein
- Synthetic tricyclic amine
- Prevent the release of infectious viral nucleic acids into host cells
- An antiparkinson agent
- A primary amine
- Antiparkinsonian
- Antihyperalgesic

- Management of Parkinson disease
- Use in the therapy of influenza A
- Derivate of adamantane
- Inhibits E-channel conductance in reconstituted lipid bilayers of SARS-CoV-2

  - Molecular Weight (g/mol) (≤500 Da): 151.25
  - Molecular formula: $C_{10}H_{17}N$
  - H-Bond Donor (≤5): 1
  - H-Bond Acceptor (≤10): 1
  - Prodrug: No
  - Chirality: Achiral Molecule
  - Rule Of Five: Yes
  - Drug type: Synthetic Small Molecule
  - ALogP:1.91
  - CX LogP:1.47
  - Aromatic Rings:0
  - Heavy Atoms:11

  - Studies involved in this research:

(Fink et al., 2021; Rosenkilde, Kledal. 2021; Kamel et al., 2021)

Oseltamivir

- Neuraminidase inhibitors
- Protease inhibitor Antivirus
- Mainly use for Influenza strain A and B
- A synthetic derivative prodrug of ethyl ester
- OTV has antiviral activity
- Earlier recovery and discharge of hospital
- Shorter length of hospital stay
- Efficient for various avian influenza virus strains
- Lower mortality rate
- Patients with ILI testing positive for coronavirus (not including SARS-CoV-2) recover sooner
- IC_{50} was 0.1–4.9 nM
- The higher the patient's average treatment duration (Oseltamivir + Hydroxychloroquine)
- The lower the average survival rate for COVID-19 patients (Oseltamivir + Hydroxychloroquine)
- Use as therapy and prophylaxis against influenza A and B
- Inhibitor of the influenza neuraminidase enzyme
- Block neuraminidases on the surfaces of influenza viruses
- Antiviral activity
- Interfere with host cell release
- Synthetic derivative prodrug of ethyl ester
- Cyclohexenecarboxylate ester
- Ethyl ester of oseltamivir acid

  - Molecular Weight (g/mol) (≤500 Da): 312.40
  - Molecular formula: $C_{16}H_{28}N_2O_4$
  - H-Bond Donor (≤5): 2
  - H-Bond Acceptor (≤10): 5
  - Prodrug: Yes
  - Chirality: Single Stereoisomer
  - Rule Of Five: Yes
  - Drug type: Synthetic Small Molecule
  - ALogP:1.29

- CX LogP:1.16
- Aromatic Rings:0
- Heavy Atoms:22

- Studies involved in this research:

(Schade et al., 2014; Govorkova et al., 2009; Asoodeh et al., 2022; Ward et al., 2005; Coenen et al., 2020; Ramatillah, Isnaini.2021)

Galidesivir (BCX-4430)

- RNA-polymerase inhibitor
- Viral RNA-polymerase inhibitor
- Antiviral use to treat hepatitis C
- A nucleoside analog
- In vitro and in vivo efficacy against several RNA viruses
- Known also as BCX4430
- An adenosine C-nucleoside analog
- Targets the RdRp of RNA viruses
- Potential treatment for filovirus infections such as Ebola virus and Marburg virus
- Potential treatment for filoviruses , coronaviruses , bunyaviruses, and arenaviruses
- Treatment for SARS-CoV-2 infection
- Similar to remdesivir (but has a nitrogen replacing the oxygen in the ribose ring)
- Broad-spectrum antiviral activity
- Block viral RdRp chain extension
- EC_{50} ranging from 3 to 68 μM
- Convert in the cell to the corresponding triphosphate nucleotide
- An adenosine analog
- Establish six hydrogen and four hydrophobic bond interactions with NSP12
- RdRp inhibitors (also Favipiravir)
- Bind to viral RdRp (Galidesivir triphosphate)
- Convert into the active triphosphate nucleotide
- Metabolize to its monophosphate form
- Antiviral activity against RNA viruses
- RNA polymerase inhibitor
- Prevent viral transcription and replication (Galidesivir triphosphate)

- Molecular Weight (g/mol) (≤500 Da): 265.27
- Molecular formula: $C_{11}H_{15}N_5O_3$
- H-Bond Donor (≤5): 6
- H-Bond Acceptor (≤10): 7
- Prodrug: Yes
- Chirality: Single Stereoisomer
- Rule Of Five: No
- Drug type: Synthetic Small Molecule
- ALogP:-1.73
- CX LogP:-2.14
- Aromatic Rings:2
- Heavy Atoms:19

- Studies involved in this research:

(Taylor et al., 2016; Dömling and Gao, 2020; Nitulescu et al., 2020; Taylor et al., 2022; Zhang W. F. et al., 2020; Nitulescu et al., 2020)

Imatinib

- Anticancer drug
- Treated certain types of cancer
- Inhibit Spike mediated viral entry
- Does not interfere with IgG formation in hospitalised COVID-19 patients
- Inhibit the early steps of SARS-CoV-2 infection
- Clinical benefit in hospitalised patients with COVID-19
- An antineoplastic agent
- Inhibit the Bcr-Abl fusion protein tyrosine kinase
- Treated chronic myelogenous leukemia
- Inhibitor of a number of tyrosine kinase enzymes
- 2-phenylaminopyrimidine derivative

  - Molecular Weight (g/mol) (≤500 Da): 493.6
  - Molecular formula: $C_{29}H_{31}N_7O$
  - H-Bond Donor (≤5): 2
  - H-Bond Acceptor (≤10): 7
  - Prodrug: No
  - Chirality: Achiral Molecule
  - Rule Of Five: Yes
  - Drug type: Synthetic Small Molecule
  - ALogP:4.59
  - CX LogP:4.38
  - Aromatic Rings:4
  - Heavy Atoms:37

  - Studies involved in this research:

(Shaul et al., 2022; Morales-Ortega et al., 2022; J Bogaard et al., 2021)

Interferon α (IFN-α) and other useful Interferon

- Antiviral activities
- Treatment of hepatitis
- Low molecular weight protein
- Used as a prophylaxis against SARS-CoV-2
- Excellent results in the rhesus macaque (combination of IFNα2b with ribavirin)
- IFNα and β are efficient in vitro
- IFNβ1b or IFNβ1a were the most potent IFN-I subtype in the inhibition of SARS-CoV and MERS-CoV
- IFNβ1a can use for severe COVID-19 patients
- IFNβ1a was superior when compared to IFNβ1b

  - Studies involved in this research:

(Lokugamage et al., 2020; Contoli et al., 2021; Chan et al., 2015; Hensley et al., 2004; Chan et al., 2013; Naghibi Irvani et al., 2021; Falzarano et al., 2013; Peiffer-Smadja et al., 2020)

Ledipasvir

- Antiviral drug
- Treatment of hepatitis C
- Use with sofosbuvir for genotype 1 Hepatitis
- Use for HCV treatment (Elbasvir, Ledipasvir, Paritaprevir, and Velpatasvir)
- Effective in treating patients with moderate COVID-19 infection (Sofosbuvir/Ledipasvir)
- SOF/LDP: accelerate time to the clinical response, but 14-day mortality; duration of hospital and ICU stay;

rate of clinical response were not different
- Ledipasvir and itraconazole can be a better for treating COVID-19 patients (coinfected with black Fungus)
- Bind to and blocks the activity of the NS5A protein
- Orally available
- Inhibitor of the hepatitis C virus (HCV)
- Treatment of chronic hepatitis C genotype 1 infection (Ledipasvir + sofosbuvir)
- A benzimidazole derivative

  - Molecular Weight (g/mol) (≤500 Da): 889.0
  - Molecular formula: $C_{49}H_{54}F_2N_8O_6$
  - H-Bond Donor (≤5): 4
  - H-Bond Acceptor (≤10): 10
  - Prodrug: No
  - Chirality: Single Stereoisomer
  - Rule Of Five: No
  - Drug type: Synthetic Small Molecule
  - ALogP:8.61
  - CX LogP:7.18
  - Aromatic Rings:5
  - Heavy Atoms:65

  - Studies involved in this research:

(Mevada et al., 2020; Balasaheb Nimse et al., 2022; Khalili et al., 2020; Seadawy et al., 2021)

Qingfei Paidu Decoction (QFPD)

- Chinese traditional medicine used to improve the lung system
- Recommend to treat all stages of COVID-19
- Qingfei Paidu decoction (QPD) and the Xuanfei Baidu decoction (XBD) have effectiveness against SARS-CoV-2 infection
- Regulating host immunity to prevent hyperinflammation (QPD and XBD)
- Decrease pro-inflammatory cytokine expression (QPD and XBD)
- Inhibit the activation of the NF-κB signaling pathway (QPD and XBD)
- Blunted pinocytosis activity in THP-1-derived macrophages (QPD and XBD)
- Robust anti-inflammatory activities in vitro (QPD and XBD)
- TCM, especially Chinese herbal medicine (CHM) fight against the COVID-19 pandemic
- No serious adverse reactions were identified
- QFPDD combined with western medicine (alpha-interferon, Oseltamivir, Chloroquine Phosphate, Arbidol, Ribavirin): more effective than the treatment of western medicine alone in the treatment of COVID-19
- Shorten the patient's hospitalization time (QFPDD combined with western medicine)
- Shorten the time of clinical symptom improvement (QFPDD combined with western medicine)
- Shorten the time of lung CT improvement (QFPDD combined with western medicine)
- QFPD is effective for treating COVID-19
- Advantages of TCM in treating emergencies
- Combination of QFPD and conventional treatment: decreasing the time for nucleic acid conversion; improving the TCM symptom scores; shortening the length of hospital stay; reducing the duration of symptoms recovery, and improving the laboratory indexes
- Combination with QFPD could improve the rate of recovery of chest CT manifestations
- TCM, especially Chinese herbal medicine (CHM), contains thousands of years of health beliefs and practical experience in China
- The effective rate of TCM exceeded 90% (confirmed COVID-19 cases) (combination of TCM and Western medicine)

  - Studies involved in this research:

(Fen et al., 2020; National Administration of Traditional Chinese Medicine, 2020; Fang et al., 2020; Li et al., 2020; Yang et al., 2020; General Office of National Health Committee, 2020; Administration of traditional Chinese medicine of JiLin province, 2021; Liang et al., 2020; Wang et al., 2020; Luo,Yang et al., 2021; Jin, 2020; Shi et al., 2020; Wang, Wang et al., 2021; Niu et al., 2021; Wang Y. et al., 2020; Xiong et al., 2020; Wu et al., 2020; Chen et al., 2020; Wu et al., 2004; Park et al., 2012; Lin et al., 2017; Sun et al., 2020; Zhou et al., 2020; General Office of National Health Committee, 2020; Ren et al., 2020; NMPA, 2021; Ge et al., 2021; Zeng et al., 2020; Fan et al., 2020)

Sofosbuvir

- Antiviral
- Treat chronic hepatitis C
- Option in the treatment of COVID-19
- Convert to its active triphosphate form by cellular enzymes
- SOF/DCV (Sofosbuvir with Daclatasvir) decrease mortality rate and need for ICU/IMV in patients with COVID-19, effective in decreasing hospital stay
- A pyrimidine nucleotide analog
- Inhibit viral replication
- Resistant to ExoN
- A HCV drug
- Inhibitor of HCV (hepatitis C virus) RNA polymerase
- Act against HCV
- An oral nucleoside analogue
- Effective against a variety of RNA viruses, including anti-SARS-CoV-2 activity in Huh7 cells
- Sofosbuvir/Daclatasvir reduced the number of patients with fatigue and dyspnoea after 1 month
- Sofosbuvir-Daclatasvir reduced the duration of hospital stay
- SOF-DCV improved clinical symptoms, oxygen saturation, and reduced ICU admission (moderate to severe COVID-19 cases)

    - Molecular Formula: $C_{22}H_{29}FN_3O_9P$
    - Molecular weight (g/mol) (≤500 Da): 529.5
    - H-Bond Donor (≤5): 3
    - H-Bond Acceptor (≤10): 11
    - Prodrug: Yes
    - Chirality: Single Stereoisomer
    - Rule Of Five: No
    - Drug type: Synthetic Small Molecule
    - ALogP: 1.66
    - CX LogP:1.28
    - Aromatic Rings:2
    - Heavy Atoms:36

    - Studies involved in this research:

(Jockusch et al., 2020; Mesci et al., 2020; Sacramento et al., 2021; Shamshirian et al., 2020; Malvi Zamzam Zein et al., 2021; Sadeghi et al., 2020; Merat et al., 2020; Khalili et al., 2020; Jockusch et al., 2020; Abbass et al., 2021)

Teicoplanin

- Antibiotic (Gram-positive bacteria)
- Use as prophylaxis
- Treatment of rheumatoid arthritis
- Treatment of systematic juvenileidiopathic arthritis
- Treatment of methicillin-resistant Staphylococcus aurenus and Enterococcus faecalis

- Immunosuppressive drug
- Isolate from a soil sample in 1978
- Extract from Actinoplanes teichomyceticus
- An antibiotic since 1986
- Used to treat Gram-positive bacterial infections
- Stop the replication of the virus
- A glycopeptide antibiotic complex
- Inhibit peptidoglycan polymerization
- Antiviral activity against SARS-CoV-2
- Inhibition of bacterial cell wall synthesis and cell death
- Isolate from the bacterium Actinoplanes teichomyceticus
- Effective at early clinical stages
- No significant antiviral effect in a study

  - Molecular Weight (g/mol) (≤500 Da): 1879.7
  - Molecular formula: $C_{88}H_{97}Cl_2N9O_{33}$
  - H-Bond Donor (≤5): 24
  - H-Bond Acceptor (≤10): 34
  - Prodrug: No
  - Chirality: Single Stereoisomer
  - Rule Of Five: No

  - Studies involved in this research:

(Vimberg et al., 2021; Ceccarelli et al., 2021)

Thalidomide

- Immunomodulators
- Increases the secretion of interleukins (IL) (such as IL-12)
- Activates natural killer cells
- An anti-inflammatory action
- Reduced the requirement for mechanical ventilation (in critical COVID-19 patients)
- Inhibiting the inflammatory cytokine surge
- Immunomodulatory properties
- Candidate for treating the complications of COVID-19
- Shorten the hospital stay length of affected patients
- Alleviate anxiety to decrease oxygen consumption
- Accelerate the negative conversion of SARS-CoV-2
- Regulate immunity
- Relieve vomit and lung exudation
- Enantiomers are converted to each other in vivo
- Racemic
- Equal amounts (both left and right handed isomers)
- Effective in improving the prognosis of patients with critical COVID-19 (Combination of Thalidomide with low dose glucocorticoid)
- Immunomodulation with Tocilizumab and Baricitinib might provide a feasible therapeutic strategy to block the progressive hyperinflammation of COVID-19

  - Molecular Weight (g/mol) (≤500 Da): 258.23
  - Molecular formula: $C_{13}H_{10}N_2O_4$
  - H-Bond Donor (≤5): 1
  - H-Bond Acceptor (≤10): 4
  - Prodrug: No
  - Chirality: Racemic Mixture
  - Rule Of Five: Yes

- Drug type: Synthetic Small Molecule
- ALogP:0.09
- CX LogP:0.02
- Aromatic Rings:1
- Heavy Atoms:19

- Studies involved in this research:

(Xia et al., 2020; Khalil, Nemer.2020; SZABO et al., 2021)

Velpatasvir

- Inhibit SARS-CoV-2 RdRp
- Sofosbuvir/velpatasvir (SOF/VEL): an anti-HCV drug; effective against SARS-CoV-2 and other families of positive-sense RNA viruses; did not reduce mortality in patients with moderate to severe COVID 19; but in mild/moderate COVID-19 seems to be safe and efficient for faster elimination of SARS-CoV-2 and to prevent disease progression
- A small molecule
- Treatment of hepatitis C (Velpatasvir + sofosbuvir)
- Direct-acting antiviral
- An orally available
- Inhibitor of the hepatitis C virus (HCV)

- Molecular formula: $C_{49}H_{54}N_8O_8$
- Molecular Weight (g/mol) (≤500 Da): 883.0
- H-Bond Donor (≤5): 4
- H-Bond Acceptor (≤10): 10
- Prodrug: No
- Chirality: Single Stereoisomer
- Rule Of Five: No
- Drug type: Synthetic Small Molecule
- ALogP: 7.73
- CX LogP: 5.57
- Aromatic Rings: 6
- Heavy Atoms: 65

- Studies involved in this research:

(Khodarahmi et al., 2021; Nevola et al., 2022)

Nitazoxanide

- Immunomodulators
- Interferes with host regulated pathways of virus replication
- Antiprotozoal activity
- Belong to thiazolides
- A synthetic benzamide
- Nitazoxanide (NTZ)
- Broad-spectrum anti-infective drug
- Amplify type I IFN pathways and cytoplasmic RNA sensing
- Broad-spectrum antiviral activity in vitro
- Decrease inflammatory cytokines
- Antimicrobial
- Activity against several parasitic worms and protozoa
- Treated protozoal and helminthic infections
- Improved viral elimination

- Shorten hospitalization time
- Reduce the expected number of hospitalizations
- Early NTZ therapy was safe and decreased viral load significantly but no difference after 5 days of therapy (In patients with mild COVID-19)
- Accelerate viral clearance
- Approve by the FDA
- Useful against SARS CoV 2
- Target endocytosis and membrane fusion, viral genome synthesis, viral release, and the inflammatory response of the SARS-CoV-2
- EC_{50} against SARS-CoV-2 was 2.12 μM in the Vero E6 cell model

  - Molecular formula:$C_{12}H_9N_3O_5S$
  - Molecular Weight (g/mol) (≤500 Da): 307.28
  - H-Bond Donor (≤5): 1
  - H-Bond Acceptor (≤10): 7
  - Prodrug: Yes
  - Chirality: Achiral Molecule
  - Rule Of Five: Yes
  - Drug type: Synthetic Small Molecule
  - ALogP:2.23
  - CX LogP:2.12
  - Aromatic Rings:2
  - Heavy Atoms:21

  - Studies involved in this research:

(Wang M. et al., 2020; Bréchot et al., 2022; Rocco et al., 202; Mahmoud et al., 2020; Zhang et al., 2021; Blum et al., 2021; Rocco et al., 2021; Mendieta Zerón et al., 2021; Lokhande and Devarajan, 2021; Sobhie Diaz et al., 2021)

Baicalein and Baicalin

- newly discovered medicine against SARS-CoV-2
- Flavonoid
- Inhibitor of HIV-1 production in vitro
- Inhibits the entry of the virus into the host cell

- **Baicalin:** natural product; bioactive; isolate from the medicinal plant Scutellaria baicalensis (SB); natural flavonoid; anti-inflammatory; therapeutic effect against SARS-CoV-2 infection; use in traditional Chinese medicine; extract from a traditional medicinal plant; glycosyloxyflavone; 7-O-glucuronide of baicalein; used for prophylaxis and treatment of hepatitis and respiratory disorders;

- **Baicalein:** a trihydroxyflavone; therapeutic drug for the treatment of COVID-19; natural product derive from S. baicalensis; use for prophylaxis and treatment of hepatitis and respiratory disorders; inhibit mitochondrial OXPHOS; a key component in TCM (Traditional Chinese Medicine) Scutellaria B.; inhibit replication of SARS-CoV-2 and VSV

  - For Baicalein:

  - Molecular Weight (g/mol) (≤500 Da): 270.24
  - Molecular formula: $C_{15}H_{10}O_5$
  - H-Bond Donor (≤5): 3
  - H-Bond Acceptor (≤10): 5
  - Prodrug: No
  - Chirality: Achiral Molecule

- Rule Of Five: Yes
- Drug type: Synthetic Small Molecule
- ALogP:2.58
- CX LogP:2.71
- Aromatic Rings:3
- Heavy Atoms:20

- Studies involved in this research:

(Dinda et al., 2017; Ha,Yang et al., 2021; Shi, Huang, Zhang. 2020; Patočka et al., 2021)

Curcumin

- Flavonoid
- Prophylactic
- Antibacterial
- Anti HIV agent
- Therapeutic drug against COVID-19
- Antiviral
- Anti-inflammatory
- Effect of curcumin on oxidative stress, glycemic profile
- Trigger humoral immunity
- Regulate cytokine storm
- Natural polyphenol
- Minimize tissue damage and vascular leakage
- Protected cellular immunity
- Nanocurcumin reduced the mortality rate
- Potential chemotherapeutic
- Antioxidant
- Reduction in clinical manifestations of COVID-19 (fever, cough, and dyspnea) was seen in the group treated with nanocurcumin (patients with mild and severe disease) (nanoencapsulated curcumin)
- well-tolerated natural compound in humans
- Anticoagulant
- Cytoprotective
- Antiplatelet
- Treatment of SARS-CoV-2 infection
- Protease inhibition
- The main constituent in Curcuma longa L. (Zingiberaceae)
- Effect on the progression of inflammatory diseases
- Inhibit the phosphorylation of IκB
- An adjuvant drug in COVID-19 treatment
- Reduce the expression of P-selectin and GP VI
- Antiplatelet effect
- Prevent platelet adhesion to the vascular endothelium
- Efficacious choice for improving COVID-19 disease outcomes

- Molecular Weight (g/mol): 368.4 (≤500 Da)
- Molecular formula: $C_{21}H_{20}O_6$
- Drug likeliness (based on Lipinski's Rule of Five): Yes
- H-Bond Donor (≤5): 2
- H-Bond Acceptor (≤10): 6
- Prodrug: No
- Chirality: Achiral molecule
- Rule Of Five: Yes
- Drug type: Synthetic Small molecule
- ALogP:3.85

- CX LogP:3.76
- Aromatic Rings: 2
- Heavy Atoms: 27

- Studies involved in this research:

(Dhar, Bhattacharjee. 2021; Paciello et al., 2020; Hassaniazad et al., 2020; Dhillon et al., 2008; Kanai et al., 2011; Gupta et al., 2013; Abbasifard, Sahebkar et al., 2022; Tahmasebi et al., 2020; Valizadeh et al., 2020; Zhang et al., 2008; Yang et al., 2013; Celes et al., 2021; Karunaweera et al., 2015; Babaei et al., 2020; Manoharan et al., 2020; Roy et al., 2020; Soni et al., 2020; Zahedipour et al., 2020; Saeedi-Boroujeni et al., 2021; Thimmulappa et al., 2021)

Galangin

- Flavonoid
- Anti HIV potential
- Interacts with 2 amino acid residues (SER-46, THR-24)
- Electrostatic interaction with HIE-41 in the main protease in COVID-19
- HIV-1 proteinase inhibitors
- A flavonol compound
- Curcumin derivative extract from the root of Alpinia officinarum
- Can induce autophagy
- Natural antioxidants with high flavonoids (lemon, green tea)
- Inhibitory for the viral infection (also Curcumin, Brazilin)
- Inhibitory for the replication (also Curcumin, Brazilin)

- Molecular Weight (g/mol):270.24 (≤500 Da)
- Molecular formula:$C_{15}H_{10}O_5$
- Drug likeliness (based on Lipinski's Rule of Five): Yes
- H-Bond Donor (≤5): 3
- H-Bond Acceptor (≤10): 5
- ALogP:2.58
- CX LogP:2.76
- Aromatic Rings:3
- Heavy Atoms:20

- Studies involved in this research:

(Pu et al., 2020; Meiyanto et al., 2020; Shakibaei et al., 2021)

Morin

- Flavonoid
- An antioxidant
- A metabolite
- Antiviral
- An antibacterial
- An anti-inflammatory
- A hepatoprotective agent
- An antineoplastic
- An antihypertensive
- A neuroprotective
- Candidate against Covid-19
- Potent inhibitor of helicobacter pylori urease
- Therapeutic potential for the treatment of COVID-19, SARS and MERS

- Molecular Weight (g/mol): 302.23 (≤500 Da)
- Molecular formula: $C_{15}H_{10}O_7$
- Drug likeliness (based on Lipinski's Rule of Five): Yes
- H-Bond Donor (≤5): 5
- H-Bond Acceptor (≤10): 7
- ALogP:1.99
- CX LogP:2.16
- Aromatic Rings:3
- Heavy Atoms:22

- Studies involved in this research:

(Dutta Choudhury et al., 2020; Ahmad et al., 2021)

Quercetin

- Flavonoid (pleiotropic molecular structure)
- Effective against Zika virus and hepatitis C
- Antiviral properties against COVID-19
- Antioxidant
- Antiviral
- Anti-inflammatory
- Lower inflammation
- Detox
- Reduced the toxic effects of COVID-19 vaccines
- Reduce the chances of being infected
- Immunoprotective effects
- Widely available plant flavonoid
- Potential anti-COVID-19 drugs
- Analgesic and inflammatory compound
- Potential treatment for severe inflammation
- Flavonoids are proven against coronavirus (including Quercetin)
- Inhibits its proteolytic activity by binding to virus-specific protease
- Inhibitory effect on platelet aggregation
- An antibacterial agent
- A protein kinase inhibitor
- An antineoplastic agent
- A ribosyl dihydro nicotinamide dehydrogenase (Quinone) inhibitor
- A phytoestrogen
- A radical scavenger
- An Aurora kinase inhibitor
- Found in many plants and foods
- Bromelain improves oral bioavailability of Quercetin up to 80% similar to vitamin C
- Potential effect of QCB (Quercetin, vitamin C, Bromelain) on the treatment of COVID-19
- Inhibits SARS-CoV-2 binding to the human cell via virus-specific protease and viral S-protein S-human ACE-2 interface
- The SARS-CoV-2 receptor binding site is similar to the binding site of SARS-CoV, as well as the SARS-Cov -2 protease, that was defined as the binding site for the hydroxyl groups of Quercetin and its derivatives

- Molecular Weight (g/mol): 302.24 (≤500 Da)
- Molecular formula: $C_{15}H_{10}O_7$
- Drug likeliness (based on Lipinski's Rule of Five): Yes
- H-Bond Donor (≤5): 5
- H-Bond Acceptor (≤10): 7
- Prodrug: No

- Chirality: Achiral Molecule
- Rule Of Five: Yes
- Drug type: Synthetic Small Molecule
- ALogP:1.99
- CX LogP:2.16
- Aromatic Rings:3
- Heavy Atoms:22

- Studies involved in this research:

(Boretti, 2021; Nair et al., 2002; Robaszkiewicz et al., 2007; Uchide et al., 2011; Saeedi-Boroujeni, Mahmoudian-Sani. 2021; Motta Junior et al., 2020; Ross JA and Kasum CM, 2002; Ferrer et al., 2008; Manach et al., 2005; Harwood et al., 2007; Puelles et al., 2020; Chen et al., 2006; Nair et al., 2002; Uchide et al., 2011; Gormaz et al., 2015; Rota et al., 2003; Zhang et al., 2020; Cui et al., 2019; ÖNAL et al., 2021; Karhausen et al., 2020; Chuammitri et al., 2017)

Scutellarein

- Flavonoid
- Antiviral
- Efficacy against coronavirus
- Inhibit SARS-CoV helicase protein

- Molecular Weight (g/mol): 286.24 (≤500 Da)
- Molecular formula: $C_{15}H_{10}O_6$
- Drug likeliness (based on Lipinski's Rule of Five): Yes
- H-Bond Donor (≤5): 4
- H-Bond Acceptor (≤10): 6
- ALogP:2.28
- CX LogP:2.40
- Aromatic Rings:3
- Heavy Atoms:21

Silibinin

- Flavonoid
- Flavonolignan
- Antiviral potential
- Isolate from milk thistle, Silybum marianum
- Antineoplastic
- Hepatoprotective
- Plant metabolite
- Antioxidant
- Candidate drug against COVID-19/SARS-CoV-2
- Anticancer properties both in vivo and in vitro
- Antioxidant
- Inhibit the invasive capacities of metastatic cells
- Natural plant polyphenol
- Treatment of lung cancer BM (alone or with radiotherapy or anticancer drugs (for lung cancer))
- Broad-spectrum efficacy against cancer
- Favorable toxicity
- Few side effects

- Molecular Weight (g/mol) (≤500 Da): 482.4
- Molecular formula: $C_{25}H_{22}O_{10}$
- H-Bond Donor (≤5): 5

- H-Bond Acceptor (≤10): 10
- Prodrug: No
- Chirality: Racemic Mixture
- Rule Of Five: Yes
- Drug type: Synthetic Small Molecule
- ALogP:2.36
- CX LogP:2.63
- Aromatic Rings:3
- Heavy Atoms:35

- Studies involved in this research:

(Mokhtarzadehbe, Baradaran et al., 2018; Bosch-Barrera, Encinar,A. Menendez et al., 2020; Deep, Agarwal. 2010; Addeo et al., 2021)

Myricetin

- Flavonoid
- Antiviral
- Anti HIV-1 potential in vitro

- Molecular Weight (g/mol) (≤500 Da): 318.23
- Molecular formula: $C_{15}H_{10}O_8$
- H-Bond Donor (≤5): 6
- H-Bond Acceptor (≤10): 8
- ALogP:1.69
- CX LogP:1.85
- Aromatic Rings:3
- Heavy Atoms:23

Epigallocatechin

- Flavonoid
- Antiviral activities of epigallocatechin-3-gallate (EGCG)
- Antiviral potential against Zika virus , renovirus
- Inhibit the replication of Coronaviruses in cell cultures
- Inhibits the enzymatic activity of the Coronavirus 3CL protease
- Regulates specific target as the viral S protein and RdRp
- Catechin primarily found in green tea
- May not be used in the treatment of COVID-19 (in the earlier stages of COVID-19)
- Ameliorate symptoms and disease severity
- Low toxicity
- Anti-inflammation
- Antioxidant
- Anti-SARS-CoV-2
- GTB or EGCG minimize the SARS-CoV-2 spread

- Molecular Weight (g/mol) (≤500 Da): 306.27
- Molecular formula: $C_{15}H_{14}O_7$
- H-Bond Donor (≤5): 6
- H-Bond Acceptor (≤10): 7
- ALogP:1.25
- CX LogP:1.49
- Aromatic Rings:2
- Heavy Atoms:22

- Studies involved in this research:

(Bimonte et al., 2021; Hu, Ho, Li, Luo. et al., 2021; Jang, Seong, Byun et al., 2021)

Abacavir

- Treatment of COVID-19
- Phosphorylates to active metabolites: inhibits the HIV reverse transcriptase enzyme competitively; acts as a chain terminator of DNA synthesis; competes for incorporation into viral DNA
- Activity against HIV-1
- A nucleoside reverse transcriptase inhibitor (NRTI)
- Inhibit RdRp (TDF (Tenofovir Disoproxil Fumarate), TAF (Tenofovir Alafenamide), ABC (Abacavir), and Lamivudine (3TC))
- Inhibit SARS-CoV-2 spike glycoprotein (combination of cobicistat-abacavir-rilpivirine HIV drugs)
- Efficient against SARS-CoV-2
- Antivirals as potential ExoN-resistant RdRp inhibitors (Cidofovir, Abacavir, Valganciclovir/Ganciclovir, Stavudine, and Entecavir)
- Approved by FAD

  - Molecular Weight (g/mol) (≤500 Da): 286.33
  - Molecular formula: $C_{14}H_{18}N_6O$
  - H-Bond Donor (≤5): 3
  - H-Bond Acceptor (≤10): 6
  - Prodrug: Yes
  - Chirality: Single Stereoisomer
  - Rule Of Five: Yes
  - Drug type: Synthetic Small Molecule
  - ALogP:1.09
  - CX LogP:0.39
  - Aromatic Rings:2
  - Heavy Atoms:21

  - Studies involved in this research:

(Tomic´ et al., 2020; del Amo et al., 2020; Smith et al., 2013)

Methylprednisolone

- Corticosteroids
- Immunomodulatory action
- Anti-inflammatory
- Suppressed cell-mediated immunologic responses
- Inhibit promoter domains of pro-inflammatory genes (Methylprednisolone–GR complex)
- Prolongs the survival time
- Prevents complication of clinical cases
- Lead to the improvement of anti-inflammatory gene product expression (Methylprednisolone–GR complex)
- Decrease mortality risk by 62%
- Corticosteroids clinically in patients with COVID-19 should be with cautions
- Methylprednisolone acetate: a 6-methyl derivative of prednisolone; an odorless; relatively white crystalline powder
- Has advantages in COVID-19 patients
- Could not improve the prognosis of patients with COVID-19
- Glucocorticoid
- Methylprednisolone surpasses dexamethasone (among hypoxic COVID-19 patients who have been hospitalized)

- Acquired from prednisolone
- Higher lung tissue-to-plasma ratio
- Low-dose is efficacious to avoid COVID-19-associated pneumonia
- FDA approved
- Less pulmonary restrictive functions
- Hospitalized COVID-19 patients might benefit from the use of MP (Methylprednisolone)
- The use of steroids for at least 5 days in severe COVID-19 is associated with a higher FVC (Forced vital capacity)
- Effectiveness by shortening hospital stay or mechanical ventilation and indicates better clinical status within 5–10 days in SARS-CoV-2-infected hospitalized patients with pneumonia (2 mg/kg/day of methylprednisolone and 6 mg/day of Dexamethasone)
- Reduced death among mechanically ventilated COVID-19 sufferers

  - Molecular Weight (g/mol) (≤500 Da): 374.5
  - Molecular formula: $C_{22}H_{30}O_5$
  - H-Bond Donor (≤5): 3
  - H-Bond Acceptor (≤10): 5
  - Prodrug: No
  - Chirality: Single Stereoisomer
  - Rule Of Five: Yes
  - Drug type: Synthetic Small Molecule
  - ALogP:1.80
  - CX LogP:1.56
  - Aromatic Rings:0
  - Heavy Atoms:27

  - Studies involved in this research:

(Scheinman et al., 1995; Wu et al., 2020; Corral-Gudino et al., 2021; Ming, Lin et al., 2020; Zhu N. et al. 2020; Annane et al., 2017; Kumar Kaushik et al., 2022; Lacerda et al., 2021; Ranjbar et al., 2021)

Ebselen

- Medicine against SARS-CoV-2
- A benzoselenazole
- Anti-inflammatory agents: non-steroidal in nature; antipyretic; platelet-inhibitory actions
- Inhibit M^{pro} activity against SARS-CoV-2
- Anti-inflammatory
- Organoselenium compound
- Cytoprotective activity
- Antioxidant
- EC_{50} (a half maximal effective concentration) of 4.67 μM
- IC_{50} (a half maximal inhibitory concentration) of 0.67 μM
- Antiviral activity against many viruses (HIV-1, Zika virus, HCV, influenza A virus)
- Exhibit hydroperoxide- and peroxynitrite-reducing activity
- Benefit in early stage SARS-CoV-2 infection
- A glutathione peroxidase
- Potential therapeutic for COVID-19 patients
- Peroxiredoxin enzyme mimetic
- Ebselen derivatives with an additional hydroxy or methoxy group are inhibitors of the viral papain-like cysteine proteases (PL^{pro})

  - Molecular Weight (g/mol) (≤500 Da): 274.19
  - Molecular formula: $C_{13}H_9NOSe$
  - H-Bond Donor (≤5): 0
  - H-Bond Acceptor (≤10): 1

- Prodrug: No
- Chirality: Achiral Molecule
- Rule Of Five: No
- Drug type: Synthetic Small Molecule

- Studies involved in this research:

(Sharun et al., 2020; Sies, Parnham. 2020; Weglarz-Tomczak, Brul.2021)

Carmofur

- Medicine against SARS-CoV-2
- EC_{50} values of 24.87 μM
- IC_{50} of 1.82 μM
- Treatment of breast and colorectal cancer
- Antineoplastic
- An antimetabolite (pyrimidine analogue)
- Treated colorectal cancer since the 1980s
- Benefit for breast, gastric and bladder cancers (clinical)
- Inhibit M^{pro} activity and against SARS-CoV-2
- Effective against a broader spectrum of viruses
- Non-specific SARSCoV-2 M^{pro} inhibitors
- Derive from 5-fluorouracil (5-FU)
- Covalently bind to the catalytic cysteine (via an electrophilic carbonyl group)
- Carmofur (1-hexylcarbamoyl-5-fluorouracil)
- Therapeutic agent for acute lung injury (ALI)
- Inhibits the M^{pro} activity (Ebselen, Disulfiram, Carmofur, α-ketoamides, and peptidomimetic aldehydes 11a/11b)

- Molecular Weight (g/mol) (≤500 Da): 257.26
- Molecular formula: $C_{11}H_{16}FN_3O_3$
- H-Bond Donor (≤5): 2
- H-Bond Acceptor (≤10): 4
- Prodrug: No
- Chirality: Achiral Molecule
- Rule Of Five: Yes
- Drug type: Synthetic Small Molecule
- ALogP:0.81
- CX LogP:1.44
- Aromatic Rings:1
- Heavy Atoms:18

- Studies involved in this research:

(Wang et al., 2020; Jin et al., 2020; Wu et al., 2019; Dai et al., 2020; Sakamoto et al., 2005; Dementiev et al., 2019; Yang, Zhang et al., 2020)

Boceprevir

- Medicine against SARS-CoV-2

- Molecular Weight (g/mol) (≤500 Da): 519.7
- Molecular formula: $C_{27}H_{45}N_5O_5$
- H-Bond Donor (≤5): 4
- H-Bond Acceptor (≤10): 5

- Prodrug: No
- Chirality: Racemic Mixture
- Rule Of Five: No
- Drug type: Synthetic Small Molecule
- ALogP:1.71
- CX LogP:1.78
- Aromatic Rings:0
- Heavy Atoms:37

Dipyridamole

- Potential COVID-19 drugs (in the virtual screening)
- Suppresses viral replication in vitro
- Bound to the SARS-CoV-2 protease M^{pro}
- Enhance immune recovery
- Suppress hypercoagulability
- Reduce viral replication
- Higher clinical remission rates
- Reduce D-dimer
- Decreased the risk of thromboembolic complications
- Inhibitor of platelet aggregation
- A vasodilator
- DIP (Dipyridamole)
- Increases lymphocytes and platelets
- A non-nitrate coronary vasodilator
- Improve clinical outcomes; increase lymphocyte and platelet recovery in the circulation (patients with COVID-19)

- Molecular Weight (g/mol) (≤500 Da): 504.6
- Molecular formula: $C_{24}H_{40}N_8O_4$
- H-Bond Donor (≤5): 4
- H-Bond Acceptor (≤10): 12
- Prodrug: No
- Chirality: Achiral Molecule
- Rule Of Five: No
- Drug type: Synthetic Small Molecule
- ALogP:-0.02
- CX LogP:1.81
- Aromatic Rings:2
- Heavy Atoms:36

- Studies involved in this research:

(Liu et al., 2020; Hong et al., 2021; Zhao, Hong, Zhang, Zhou, Luo et al., 2020)

Pongamoside D (Hyoscyamus Niger)

- Inhibitor against SARS-COV-2 disease

- Molecular Weight (g/mol) (≤500 Da): 474.4
- Molecular formula: $C_{23}H_{22}O_{11}$
- H-Bond Donor (≤5): 4
- H-Bond Acceptor (≤10): 11

Peonidin (Brassica Nigra)

- Inhibitor against SARS-COV-2 disease
- An anthocyanidin cation
- Anthocyanins are: Flavonoid compounds; natural pigments; responsible for a wide range of colors in fruits, vegetables and flowers; consisting of two aromatic rings (separated by a heterocyclic ring with an oxygen cation); Cyanidin, Delphinidin, pelargonidin, Peonidin, Petunidin, and malvidin are common types of anthocyanidins
- Chemically, Anthocyanidins are grouped into 3-Hydroxyanthocyanidins, 3-Deoxyanthocyanidins, and O-Methylated Anthocyanidins
- Delphinidin-3-O-glucoside and peonidin-3-O-glucoside might have function as anti-inflammatory factor related with TNF-α signaling

    - Molecular Weight (g/mol) (≤500 Da): 301.27
    - Molecular formula: $C_{16}H_{13}O_6^+$
    - H-Bond Donor (≤5): 4
    - H-Bond Acceptor (≤10): 5
    - ALogP:3.21
    - CX LogP:3.08
    - Aromatic Rings:3
    - Heavy Atoms:22

    - Studies involved in this research:

(Fatchiyah et al., 2019; He et al., 2018; Khoo et al., 2017)

Bacillus Calmette-Guérin (BCG)

- Tuberculosis prevention
- Prevent severe COVID-19
- Inhibit a TGF-β1-mediated EMT
- A vaccine derived from the live attenuated strain of Mycobacterium bovis
- Potential adjuvant
- Decreased sickness of SARS-CoV-2 infection
- Safe alternative
- Use as a vaccination against tuberculosis
- Lower hospitalisation rate
- Heterologous immune effects
- Boosts the immune system against SARS-CoV-2

    - Studies involved in this research:

(Weng et al., 2020; Ochando et al., 2021; Adesanya, Ebengho. 2020; O'Conner et al., 2020)

Warfarine

- Use against virulent proteins of SARS-CoV-2
- Inhibit vitamin K production
- A Vitamin K antagonist
- Anticoagulant effect
- Require close monitoring to ensure safety and efficacy
- An odorless and colorless solid
- Has a narrow therapeutic range
- Prevents blood clot formation (also migration)

- No proof of harmful effects on severe COVID-19 disease
- Anti-vitamin K activity
- Oral anticoagulant
- Lower doses needed to achieve therapeutic anticoagulation

  - Molecular Formula: $C_{19}H_{16}O_4$
  - Molecular weight (g/mol): 308.3 (≤500 Da)
  - H-Bond Donor (≤5): 1
  - H-Bond Acceptor (≤10): 4
  - Prodrug: No
  - Chirality: Racemic Mixture
  - Rule Of Five: Yes
  - Drug type: Synthetic Small Molecule
  - ALogP:3.61
  - CX LogP:2.74
  - Aromatic Rings:3
  - Heavy Atoms:23

    - Studies involved in this research:

(Irwin et al., 2021; Wong et al., 2021; Emren et al., 2021)

Aspirin

- Anticoagulants
- Antiplatelet drug
- Antiviral properties
- Salicylic acid (Aspirin)
- Inhibit the cyclooxygenase enzyme (COX), which exhibits two forms: COX-1 and COX-2
- Anti-inflammatory
- Produce via different routes
- Antipyretic
- Administer in various doses and forms
- Part of the treatment Kawasaki disease
- Impacts various disease-relevant pathways
- Analgesic
- Pharmacologic agent to treat COVID-19
- Treatment of pain and fever
- Acetylsalicylic acid (ASA)
- Inhibit platelet aggregation
- Prevent blood clots stroke
- Antithrombosis
- Inhibition of COX
- Inhibition of IKK kinase

  - Molecular Formula: C_9H8O_4 ($CH_3COOC_6H_4COOH$)
  - Molecular weight (g/mol): 180.16 (≤500 Da)
  - H-Bond Donor (≤5): 1
  - H-Bond Acceptor (≤10): 4
  - Prodrug: No
  - Chirality: Achiral Molecule
  - Rule Of Five: Yes
  - Drug type: Synthetic Small Molecule
  - ALogP: 1.31
  - CX LogP:1.24
  - Aromatic Rings:1

- Heavy Atoms:13

- Studies involved in this research:

(Arabi et al., 2022; Rife and Gedalia, 2020; Arif and Aggarwal, 2021; Patrono et al., 2001; Tantry et al., 2021)

Chinese medicine against MERS-CoV
Fruits and twigs of Aglaia foveolate

Chinese medicine against SARS-CoV-2
Licorice, Ephedra, Bupleurum root, Astragalus, Panax ginseng

Chinese medicine against SARS-CoV
Glycyrrhiza radix
Lycoris radiata
Salvia miltiorrhiza

Monalizumab

- Mono clonal antibody targeting NKG2A
- Abrogated NKG2A inhibitory
- Block mAb
- Increases degranulation and IFN-γ production by $NKG2A^+$ NK cell
- A humanized anti-NKG2A
- A humanized IgG_4 antibody
- An inhibiting antibody against NKG2A
- Successfully ceasing tumor progression (no significant side effects)
- Restored the function of CD8+T and NK cells in cancers

- Studies involved in this research:

(Vivier et al., 2019; Paggi et al., 2020; Sordo-Bahamonde et al., 2021; Yaqinuddin, Kashir. 2020)

Rapamycin

- Inhibitor of viral replication
- Inhibit the mTOR
- Candidate for COVID-19 therapy
- Use a low dosage of Rapamycin may be considered as a therapy to treat COVID-19
- P13K/mTOR inhibitor
- A macrolide immunosuppressant
- Anticancer activity (shown in the 1990s)
- Prevents the activation of lymphocytes
- Block mTOR enzyme
- Immunosuppressive activity
- Sirolimus (Rapamycin)
- Antifungal
- Antitumour effects
- A macrocyclic lactone
- Presents in soil actinomycete Streptomyces hygroscopicus
- Found in a sample of mud
- Macrocyclic antibiotic
- Prevents cellular rejection after renal transplantation (alone or in combination with calcineurin inhibitors and corticosteroids)

- Molecular Weight (g/mol): 914.2 (≤500 Da)
- Molecular formula: $C_{51}H_{79}NO_{13}$
- H-Bond Donor (≤5): 3
- H-Bond Acceptor (≤10): 13
- Prodrug: No
- Chirality: Single Stereoisomer
- Rule Of Five: No
- Drug type: Synthetic Small Molecule
- ALogP:6.18
- CX LogP:7.45
- Aromatic Rings:0
- Heavy Atoms:65

- Studies involved in this research:

(Kuca et al., 2021; Husain,N. Byrareddy. 2021)

Nafamostat

- a serine protease inhibitor
- Nafamostat Mesylate (Nafamostat)
- a synthetic protease inhibitor
- fast-acting proteolytic inhibitor
- inhibits the activities of a variety of proteases
- broad-spectrum
- antiviral activities
- anti-inflammatory effect in vitro
- blocks the activation of trypsinogen to trypsin
- mucus clearing
- decrease epithelial sodium channel (ENaC) activity
- increase mucus clearance in the airways
- formulated with hydrochloric acid
- used during hemodialysis
- inhibiting several serine proteases including thrombin
- improves acute pancreatitis
- prevents blood clot formation
- prevent the proteolysis of fibrinogen into fibrin
- treat pancreatitis
- blocks TMPRSS2 activity
- treatment of disseminated intravascular coagulation and pancreatitis
- an anticoagulant
- Nafamostat and VR23 interplay with the critical binding site residues of $3CL^{pro}$ and PL^{pro} of SARS-CoV-2 and possibly inhibit the growth of SARS-CoV-2 by targeting $3CL^{pro}$ and PL^{pro}
- no difference in time to clinical improvement between the Nafamostat and SOC groups, but a shorter median time to clinical improvement in a small group of high-risk COVID-19 patients requiring oxygen treatment
- In hospitalised patients with COVID-19, did not observe evidence of anti-inflammatory, anticoagulant or antiviral activity with intravenous Nafamostat, and there were additional adverse events
- reduce the viral entrance
- block MERS-CoV infection in vitro
- suppressing membrane fusion between the virus and human cells (MERS-CoV)

- Molecular Weight (g/mol): 347.4 (≤500 Da)

- Molecular formula: $C_{19}H_{17}N_5O_2$
- H-Bond Donor (≤5): 4
- H-Bond Acceptor (≤10): 4
- Prodrug: No
- Chirality: Achiral Molecule
- Rule Of Five: Yes
- Drug type: Synthetic Small Molecule
- ALogP:2.65
- CX LogP:2.52
- Aromatic Rings:3
- Heavy Atoms:26

- Studies involved in this research:

(Kumar et al., 2021; Asakura and Ogawa, 2020; Hoffmann et al., 2020; Bae et al., 2021; Zhuravel et al., 2021; Dhaliwal et al., 2022; Bae et al., 2021; Yamamoto et al., 2016)

Sulfadoxine

- Sulfadoxine-Pyrimethamine (SP) is used to treat malaria
- A sulfa medicine
- Inhibits the enzyme dihydropteroate synthetase
- Bacteriostatic
- A synthetic analog of PABA (para-aminobenzoic acid)
- Compete with PABA for the bacterial enzyme dihydropteroate synthase
- Antimalarial
- Broad-spectrum sulfanilamide

- Molecular Weight (g/mol): 310.33 (≤500 Da)
- Molecular formula: $C_{12}H_{14}N_4O_4S$
- H-Bond Donor (≤5): 2
- H-Bond Acceptor (≤10): 8
- Prodrug: No
- Chirality: Achiral Molecule
- Rule Of Five: Yes
- Drug type: Synthetic Small Molecule
- ALogP: 0.88
- CX LogP: 0.58
- Aromatic Rings: 2
- Heavy Atoms:21

- Studies involved in this research:

(Bell et al., 2008)

OTHER THERAPIES:

DEXAMETHASONE:

- Crystalline white powder
- Odorless
- Water-Insoluble
- Decrease hemolysis
- Anti-inflammatory
- Readily absorbed if taken orally

- Highly bound to albumin
- Synthetic adrenal corticosteroid
- Interferes with NF-kB activation
- FDA approval
- Bind to specific nuclear steroid receptors
- Reduce severity among COVID-19 patients
- Promote heme oxygenase (HO)-1 in macrophages
- A fluorinated steroid

(Vallelian et al., 2010; Fernandes et al., 2019; Rohdewald et al., 1987; Peterson 1959)

GLUCOCORTICOIDS:

- Acts as a modulator of multiple biological activities in immune cells
- Provide both stimulation and inhibition of the immune reaction
- Have been shown to cure disorders closely similar to COVID-19, SARS, MERS, community-acquired pneumonia, and severe influenza
- May depending on their dosage in the blood and the duration of time that drugs are administered

(Strehl et al., 2019; Singh et al., 2020; Siemieniuk et al., 2015; Arabi et al., 2018; Lansbury et al., 2020)

INTERFERON

- IFNβ1b or IFNβ1a were the most potent IFN-I subtype in the inhibition of SARS-CoV and MERS-CoV
- Combination of IFNβ with Lopinavir/Ritonavir against MERS-CoV improved pulmonary function but did not considerably reduce virus replication or lung pathology severity
- Combination of IFNα2a with Ribavirin delayed mortality without reducing it on the long run
- Combination of IFNα2b with Ribavirin gave excellent results in the rhesus macaque but was inconclusive in human
- Positive effect of IFN-I treatment on SARS-CoV
- IFNβ is a more potent inhibitor of coronaviruses than IFNα
- A study shows that IFNβ1b was as effective as Lopinavir/Ritonavir against MERS-CoV in marmosets
- IFNβ1 may account for a safe and easy to upscale treatment against COVID-19 in the early stages of infection
- IFN-I can be used as a prophylaxis against SARS-CoV-2

(Sheahan et al., 2020; Omrani et al., 2014; Falzarano et al., 2013; Arabi et al., 2017; Loutfy et al., 2003; Zhao et al., 2003; Scagnolari et al., 2004; Stockman et al., 2006; Hensley et al., 2004; Chan et al., 2013; Dong et al., 2020; Hart et al., 2014; Chan et al., 2015; Lokugamage et al., 2020; Peiffer-Smadja et al., 2020)

CORTICOSTEROID

- Anti-inflammatory
- Accessible
- Easy to employ

(Fadel et al., 2020; Salvi and Patankar, 2020; Wang D. et al., 2020; Xu et al., 2020)

MOLNUPIRAVIR:

- Isopropyl prodrug
- Nucleoside analog β-D-N4-hydroxycytidine

- Isopropylester prodrug of [N4-hydroxycytidine]
- Broad-spectrum antiviral activity
- Hydrolyzed in vivo
- A ribonucleoside analogue
- Distribute into tissues (active 5'-triphosphate form)
- Molnupiravir (EIDD-2801, MK-4482)
- Antiviral agent
- Target the RdRp
- IC_{50} against SARS-CoV-2 was 0.3 and 0.08 μM in Vero and Calu-3 cells
- CC_{50} >10 μM
- Prevent and treat SARS-CoV-2, SARS-CoV, and MERS-CoV
- Reduce viral load
- Prevent virus transmission through direct contact with untreated animals

(Sheahan et al., 2020; Wahl et al., 2021; Cox et al., 2021)

AZVUDINE:

- A Reverse transcriptase inhibitor
- HIV treatment
- Shorten the nucleic acid negative conversion time (in patients with mild or common COVID-19)
- Novel nucleoside analog
- A nucleoside reverse transcriptase inhibitor
- Treat hepatitis C patients
- RdRp inhibitor
- Conversion to triphosphate in vivo
- Act against HIV, HBV, and HCV

(Yu and Chang, 2020; Smith et al., 2009; Ren et al., 2020)

TENOFOVIR/EMTRICITABINE:

- Prevention of HIV infection
- An approved drug
- Bind tightly to SARS-CoV-2 RdRp
- Termination of strand synthesis
- Incorporate as a substrate into the nascent RNA strand

(Jockusch et al., 2020; Elfiky, 2020)

TRIAZAVIRIN:

- No significant benefit for patients with COVID-19
- Purine nucleoside base analog
- Anti-SARS-CoV-2 effects as a $3CL^{pro}$ inhibitor
- Treat flu patients
- Broad-spectrum antiviral activity
- Approved for the treatment of influenza
- A guanine nucleotide analog
- Inhibiting viral RNA synthesis
- Inhibiting replication of viral genome fragments

- A small, insignificant benefit in treating COVID-19 patients

(Wu X. et al., 2020; Shahab and Sheikhi, 2020; Karpenko et al., 2010; Rusinov et al., 2015; Wu et al., 2020)

NICLOSAMIDE:

- FDA-approved
- An anthelmintic drug
- Anti-SARS-CoV-2 activity in Vero E6 cells
- Antineoplastic activity
- A piscicide
- An apoptosis inducer
- A molluscicide
- An anticoronaviral agent
- A STAT3 inhibitor
- Chlorinated salicylanilide
- An orally bioavailable
- Did not reduce mortality from SARS-CoV-2 infection
- Reduce the time needed for recovery from SARS-CoV-2 infection
- Inhibit viral entry into cells by affecting pH-dependent endocytosis
- An antiparasitic agent
- Reduce receptor-binding domain

(Jeon et al., 2020; Prabhakara et al., 2021; Abdulamir et al., 2021)

CHLORPROMAZINE:

- A psychotropic agent
- Strong antiadrenergic activity
- Weaker peripheral anticholinergic activity
- A phenothiazine
- Antipsychotic agent
- Treatment of schizophrenia
- Sedative and antiemetic activity
- FDA-approved
- Broad-spectrum antiviral activity
- IC_{50} value of Chlorpromazine against SARS-CoV-2 was about 9–10 μM
- A study said that Chlorpromazine impedes the clathrin-mediated endocytosis pathway by inhibiting the relocalization of clathrin and adaptor protein 2 on the cell surface, thus inhibiting SARS-CoV entry
- Immunomodulatory effects
- Antiviral effects
- Increase IgM levels in the blood
- Treat psychiatric disorders

(Plaze et al., 2021; Inoue et al., 2007; Plaze et al., 2020)

PROXALUTAMIDE:

- An androgen receptor antagonist
- Inhibit androgen receptor function
- Block the SARS-CoV-2 entry
- Accelerated viral clearance

- Used to treat prostate cancer
- Reduced the time of clinical symptom alleviation (in patients with mild to moderate COVID-19)
- Downregulation of ACE2 and TMPRSS2 expression at the transcriptional level

(Wu S. et al., 2020; Cadegiani et al., 2021)

FLUVOXAMINE:

- Anti-inflammatory effects
- Anxiolytic properties
- A 2-aminoethyl oxime ether of aralkylketones
- Selectively blocks serotonin reuptake
- FDA approved
- Inhibit the serotonin reuptake pump
- Therapy of obsessive-compulsive disorder
- A selective serotonin reuptake inhibitor (SSRI)
- Reduce the need for hospitalization among high-risk outpatients
- Reduce production of immunomodulatory cytokines
- Treatment of obsessive-compulsive disorder and depression
- Bind to S1R
- Antiviral effects by affecting the S1R-IRE1 pathway
- Antiviral effects through its lysosomotropic properties
- Exerted its anti-SARS-CoV-2 effects by inhibiting acid sphingomyelinase
- Reduce the expression level of inflammation-related genes

(Reis et al., 2022; Rafiee et al., 2016; Rosen et al., 2019; Lenze et al., 2020; Kornhuber et al., 2021)

PLITIDEPSIN:

- A cyclic depsipeptide approved
- A didemnin
- Candidate drug for COVID-19 treatment
- Treatment of patients with refractory multiple myeloma

(Zhong, Li., 2022)

APILIMOD:

- A small-molecule inhibitor of PIKfyve
- Anti-SARS-CoV-2 activity
- IC_{50} values of 0.007 μM and <0.08 μM
- Inhibit PIKfyve phosphorylation in SARS-CoV-2 infection
- Interfere with endosome transport
- Prevent virus entry
- Inhibit PIKfyve activity

(Bouhaddou et al., 2020; Kang et al. 2020)

AZITHROMYCIN:

- (AZM) is a semisynthetic macrolide antibiotic
- In vitro EC_{50} for AZM against SARS-CoV-2 was 2.12μM
- EC_{90}: 8.65μM
- Induce reduction in Rhinovirus replication 7-fold in primary bronchial epithelial cells
- Belong to the azalide class
- Treatment of Mycobacterium avium intracellulare infections, toxoplasmosis, and cryptosporidiosis
- Structurally related to ERYTHROMYCIN
- Bactericidal effects
- Inhibits influenza, Zika, Dengue, and Ebola viruses
- Target the protein synthesis process of bacteria
- Did not provide any beneficial effect (in treating COVID-19 patients)

(Ballow and Amsden, 1992; Damle et al., 2020; Wang M. et al., 2020; Schögler et al., 2015; Hughes et al., 2020; Rodríguez-Molinero et al., 2020; Furtado et al., 2020; Cavalcanti et al., 2020)

TENOFOVIR:

- No efficacy in vitro nor in vivo
- Binds tightly to the RdRp of SARS-CoV-2
- Therapy of HIV (in combination with other agents)
- An acyclic nucleotide analogue of adenosine
- Use in tenofovir-based microbicides
- Therapy of hepatitis B virus (HBV) infection
- Nucleoside Reverse Transcriptase Inhibitors (NRTIs) (a class of HIV drugs)
- NRTIs block an HIV enzyme (reverse transcriptase)
- By blocking reverse transcriptase, NRTIs prevent HIV from multiplying and from spreading to other cells
- Tenofovir disoproxil fumarate (Viread) is an anti-retroviral used to treat HIV patients

(Desai et al., 2017; Elfiky, 2020; Choy et al., 2020; Park et al., 2020)

BALOXAVIR MARBOXIL:

- Baloxavir Marboxil (Xofluza)
- Treat flu
- Inhibits the endonuclease activity of the PA subunit
- Ineffective in vitro against SARS-CoV-2 (SARS-CoV-2 encodes its own capping enzyme)
- Very effective
- Fast-acting
- An orally bioavailable prodrug
- Influenza cap-dependent endonuclease (CEN) inhibitor
- Antiviral activity
- Convert by hydrolysis to its active metabolite baloxavir
- Therapeutic activity against influenza A and B virus infections
- Prevent polymerase function (Therefore influenza virus mRNA replication)
- Inhibit an enzyme required for viral replication
- Target the virus polymerase complex
- Preventing cap-snatching (Hence viral mRNA synthesis)
- One oral dose is enough

(Noshi et al., 2018; Hayden et al., 2018; Choy et al., 2020; Wang et al., 2020)

TCM:

- Mortality rate of cases is lower
- Found to be safe for patients with COVID-19
- May not promote the negativity of the SARS-CoV-2 nucleic acid
- TCM (Traditional Chinese Medicine)
- Averrhoa Carambola L. is a valuable treatment in Chinese medicine with therapeutic potential for multiple diseases
- Althaea officinalis, Commiphora molmol, Glycyrrhiza glabra, Hedera helix, and Sambucus nigra can use in the treatment of early/mild cases of COVID-19

(Li et al., 2021; Shu et al., 2020; He, Zeng et al 2021; Wei et al., 2014; Silveira, Prieto-Garcia, Heinrich et al., 2020)

Table 2[5] [71] [72] [73] [74] [75] [76] [77] [78] [79] [80] [81] [82] [83] [84] [85] [86] [87] [88] [89] [90] [91] [92] [93] [94] [95] [96] [97] [98] [99] (As we can't evaluate all of the Therapies stated in this table as like as the ivermectin, so we first stated the important record of each therapy, and it should be considered that if there are two sentences in each therapy that contrary to each other only reflect the findings from studies that conducted to evaluate that therapy. Administration of this kind of therapy that has these sentences should be carefully)

[5] Some Of The Data Acquired From https://pubchem.ncbi.nlm.nih.gov https://www.kegg.jp/ https://www.ebi.ac.uk/chembl/ ClinicalTrials.gov

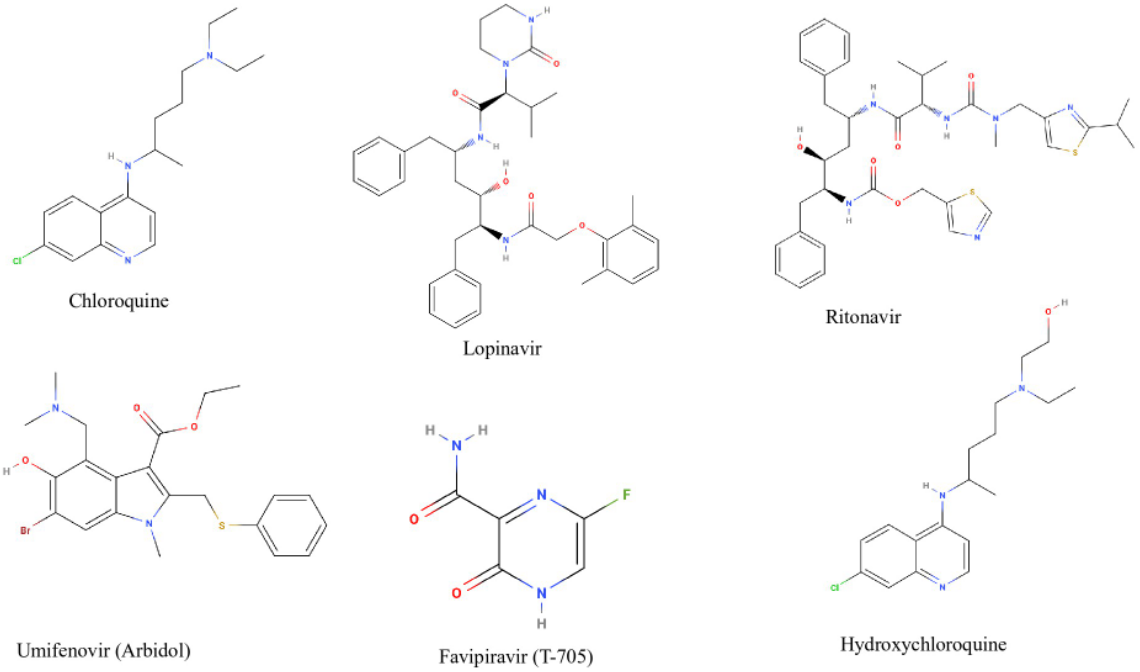


Figure 3[6] (Many drugs with different properties have common effects because they have similarities in their chemical structures and can bind to a single receptor)

4. Discussion

In general, it should be noted that you need to do the previously mentioned test to determine whether ivermectin is effective or not. In fact, one needs to increase the statistical population to prove that this drug does not have placebo properties. An experiment should be created where there are two groups, and the first group should receive the same drug, and it should be said that it is a drug and does not have many therapeutic properties. The second group should receive the same drug and patients should be informed that this drug has therapeutic properties. If this drug (Ivermectin) is a useful drug for coronavirus, it should be useful for both, otherwise it's just a placebo. But the interesting thing is that ivermectin originated in the soil in the first place. Professor Satoshi Omura isolated an unusual Streptomyces bacterium in soil with William

[6] Figures from https://molview.org

Campbell in 1975 and discovered that the bacterial culture could cure mice infected with the roundworm Heligmosomoides polygyrus. Campbell isolated the active ingredients from bacterial culture and named them "avermectins" (Crump and Omura, 2011).

4.1. Ivermectin - Is It Effective?

Before the Corona outbreak, an article was published that did not cover much and cited soil as a strategy to combat both bacterial and viral diseases [108]. The interesting thing is that today we know that ivermectin is effective in the fight against the coronavirus. Other drugs, such as teicoplanin and cyclosporine and rapamycin effective against Coronavirus, actually come from the soil. Ciclosporin was first isolated from the Tolypocladium inflatum (T. inflatum) fungus in soil samples in 1969 (Beauchesne et al., 2007). Additionally, cyclosporine suppresses immune system activity by inhibiting T-cell activity and growth (Liddicoat & Lavelle, 2019) and IL-6 production (Stephanou et al., 1992). Teicoplanin was first described in 1978 and extracted from Actinoplanes teichomyceticus isolated from a soil sample (Vimberg et al., 2021). The scientific reason for our conference is a study that a French scientist has already carried out.

In 1927 Dubos[7] searched for a microbe that could break down the polysaccharide capsule of a deadly bacterial pneumonia in the same way soil bacteria digest decaying organic matter in forests. Dubos wondered how soil could kill germs. How come a patient with tuberculosis or the plague disappears soon after his funeral, the same germs that killed him? [100][101][102][103][104][105][106][107]. It would be great here to reference a religious position that says God created the disease and also created medicine for the disease. The healing property of a medicine is of God, and God adds that property, not us.

Something to add here is: The religion of Islam has offered an interesting solution that is worth noting. In fact, this solution has already arrived, and the result is positive, and it is reading a prayer that can of course protect you from diseases, while following health protocols. And this prayer is the Ziyarat Ashura.

4.2. Miracles of Ziyarat Ashura

The deceased Ayatollah Dastgheib states in his book: Allama Sheikh Hassan Farid Golpayegani quoted his teacher, the deceased Ayatollah Sheikh Abdul Karim Haeri Yazdi:
While I was studying religious sciences in Samarra, the people of Samarra contracted cholera and plague, and some people died every day. One day, we were at the house of my deceased teacher, Seyyed Muhammad Fesharaki, with a group of scholars. Cholera is a disease that everyone is at risk of dying from. The deceased Mirza said: If I give a verdict, is it necessary to do it or not? All the members that were there acknowledged that, yes. Then he said: I order the Shiites living in Samarra to be engaged reading the Ziyarat Ashura from today to ten days, and to reward it as a gift to the honorable soul of Narjis Khatoon, the mother of Muhammad Ibn al-

[7] https://en.m.wikipedia.org/wiki/Ren%C3%A9_Dubos
https://en.m.wikipedia.org/wiki/Tyrothricin

Hasan al-Mahdi (AS) (Imam Mahdi, known as al-Qaem (The Riser)) so that this calamity may be removed from them. The verdict was conveyed to all Shiites and everyone started performing Ziyarat Ashura. From the day after the end, the disappearance (death) of the Shiites stopped and the non-Shiites died every day, so that it became clear to everyone that some of them asked their acquaintances about the Shiites: What is the reason why they are no longer people dying from you? They were told: Ziyarat Ashura, they (non-Shiites) were also engaged in reading that prayer and the calamity was removed from them.
Allama Farid said:
When I was in a difficult situation, I remembered the order of the deceased, and from the first of Muharram, I was engaged in the Ziyarat Ashura, and on the eighth day a miracle occurred, and I overcame that difficult situation.[8]

It is also important to say that there are people who still do not believe in the existence of COVID-19, calling it a sham or a hoax, much like the story of the National Football League, where a group of scientists is at the helm. One of them was Mr. Omalu who presented a case of chronic traumatic encephalopathy in a retired player [109] and even confirmed by the autopsy that some people blamed him and his group and at first they didn't believe it, but eventually they accepted it. Here, some people not only believe in coronavirus, but also say that there is no virus on earth at all. In the end, we will see that people have accepted that coronaviruses like CTE exist. Unfortunately, these issues are reflected in the global media. We even see that people and even hospital staff have prescriptions that tell them what drugs to take if they don't get Corona or if they have the virus, these recipes will improve your immune system. Of course, these prescriptions had no scientific basis. For example, we can refer to the following prescription:

Vitamin C 1000 mg twice per day / Vitamin D_3 1000-3000 IU once daily / Quercetin 250 mg once daily / Zinc 50 mg once daily / Melatonin 6 mg at bedtime / Ivermectin

It is better for people to avoid prescriptions that have no scientific basis and follow news and authoritative material from official sources, not in places where it is not clear where the news is coming from, and sadly some people like to hear it, Coronavirus is man made rather than from nature. They like to follow the news on social media instead of reliable sources, or they like to spread the word about the dangers of vaccines instead of their safety, but not all people. Or even if the disease spreads, we get help from scientists who give them fewer wages and more wages in other fields and jobs. Indeed, after the end of working hours in universities and science centers, the work of scientists does not end like other careers. In fact, they take the work home with them when they finish work. In fact, most of the work of scientists is done with their salary. Most scientific discoveries are made without the help of governments. We should be grateful to the scientists who did scientific work before us, as well as to the scientists who found medicine and died during the Corona period, but their memories are still alive. It doesn't matter that some people don't pay attention to what scientists say. Scientists always do their work with enthusiasm and do their best, but we should beware of scientists who work under the guise of scientists and

[8] From the book :Wonderful Stories, The Deceased Ayatollah Dastghib

do inhumane things. We focus on scientists who want to take responsibility and improve people's situation, and make people live in a peaceful place, away from any harm caused by diseases.

5. Conclusion:

Finally, in this article, we looked at the effects of ivermectin on coronavirus and patients in three ways. The first research strategy highlighted the effectiveness of this drug, and we reviewed and asked about its strengths and weaknesses. In the second strategy, we focused on research that indicated the ineffectiveness of this drug, and finally, the third strategy was to combine this drug with other drugs. In general, we believe that the reason ivermectin is useful is that it goes back to its origin, which is the soil. Our theory and hypothesis is that if the coronavirus, whether made by humans or by nature, can generally be treated with nature, which is soil. In the following, we discussed and organized other potential therapies that were discovered before, and we reviewed them in Table 2. We hope that this article has been able to take a step in finding a corona drug, InshaAllah.

Limitations

It is important to recognize the limitations of this study. Although careful research has been done to gather data, other relevant and important studies may have been overlooked. Finally, it is important that the review was limited to English studies. There are likely many other relevant studies in other languages that have not been reviewed in this study.

6. Declarations:

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Consent To Publish: Not Applicable

Data Transparency: The datasets generated during the current study are available from the corresponding author on reasonable request.

Code Availability: Not Applicable

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design. The author wrote the first and final draft and read the final manuscript also data collection and analysis performed by the corresponding author.

7. Abbreviations :

RNA: Ribonucleic acid

RT-qPCRs: Real-time reverse-transcription polymerase chain reaction assays

IC_{50}: Half maximal inhibitory concentration

EC_{50}: Half-maximal effective concentration

RT-PCR: Reverse transcription polymerase chain reaction

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

FDA: The American Food and Drug Administration

MV: Mechanical ventilation

IL-6: Interleukin-6

COVID-19: Corona virus disease 2019

MHV: Mouse Hepatitis Virus

CP: convalescent plasma

CPT: convalescent plasma trans-fusion

PCR: polymerase chain reaction

RT-PCR: real-time polymerase chain reaction

JAK inhibitor: Janus kinase inhibitor

IgG: Immunoglobulin G

IVM: Ivermectin

ARBs: Angiotensin II receptor blockers

ACEIs: Angiotensin-converting enzyme inhibitors

HCoVs: Human corona viruses

SOC: standard of care

NP: natural product

RCT: Randomized Controlled Trial

AEs: adverse events

TMEM16A: Transmem-brane protein 16A

GI: gastrointestinal

CTE: Chronic Traumatic Encephalopathy

ACE-2: Angiotensin-converting enzyme 2

TMPRSS2: Transmembrane Serine protease 2

RdRp: RNA dependent RNA polymerase

FPV: Favipiravir

RBV: Ribavirin

UFV: Umifenovir

OTV: Oseltamivir

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