

Review Article

As Drugs Assemble to Treat SARS-COV-2, Which Drug will Prove Efficacious : A Search for Suitable Drug or Vaccine to Manage COVID-19 Pandemic

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ABSTRACT

COVID-19 literally ambushed humanity and took the medical world by surprise with no adequate arrangement to manage it in terms of appropriate drugs and vaccine as the origin of the disease still remains a mystery. There has been aggressive search for an appropriate drug that will bring this pandemic with high mortality under control. This study took time to carry out a literature search on the drugs and medications so far tried on COVID-19 patients since its outbreak in Wuhan China to date. We carried out search on Medline, PubMed, SciElo, Google scholar, among others on drugs used for SARS-COV-2 infections and some of the documented outcomes. The study found a constraint in time by researchers to carry out a comprehensive study on any of the drugs since the disease was causing high mortalities across the globe. Most of the drugs that appeared beneficial and non-beneficial in treatment of SARS-COV-2 infections did not use adequate samples enough to draw statistically significant inferences. At the moment, high-impact treatment options for COVID-19 are; Antiviral drugs, Anti-inflammatory drugs, ACE inhibitors and angiotensin receptor blockers, Hydroxychloroquine + Azithromycin and convalescent serum among several other options including COVID organics. We however recommend that treating Physicians are at liberty to use appropriate combination of medications at their disposal based on information provided below as we lack sufficient proof to make any drug recommendation. This may possibly reduce the rates of disease progressions from mild into severe disease requiring intensive care and ventilators.

Keywords: COVID-19, Drugs, SARS-COV-2, Treatment

BACKGROUND

It was in 1965 when Tyrrell and Bynoe isolated a virus named B184 in human embryonic tracheal organ cultures obtained from respiratory tract of adults with common cold. Also Hamre and Procknow isolated a virus they labeled 229E from tissue cultures of medical students who were suffering from common cold symptoms. Both viruses were ether-sensitive but instinctively different from all the ortho- and paramyxoviruses. In a similar manner McIntosh and colleagues isolated several strains of ether-sensitive viral particles from human respiratory tract which they labeled OC.^{1,2}

Electron microscopic studies carried out by Almeida and Tyrrell on these viruses coupled with their serological properties showed that they were distinct with unique morphological features. They are medium sized (80-

150nm), pleomorphic, membrane coated, and are covered with widely-spaced club-shaped surface projections. The viruses were then assigned distinctive viral group called Coronaviruses meaning crown-like appearance of the surface projections of the viruses.²⁻⁴

Coronaviruses have remained zoonotic for the most part associated with several infections such as: feline and canine interstitial pneumonias in wild cats and dogs, bovine pneumoenteric infections in cows, calf diarrhea and calf respiratory BCoV infections, winter dysentery BCoV infections in adult cattle, shipping fever BCoV infections, a respiratory disease in feedlot cattle, feline CoV (FCoV) infectious pneumonitis, and Coronavirus infectious bronchitis (CoVIB), respiratory disease in chickens (See Table below). These diseases had caused severe economic and agricultural losses in the past with very little or limited history of transmission to man with severe consequences.

Table showing various animal corona viruses⁷

Genetic Group	Virus	Host	Disease/Infection Site		
			Respiratory	Enteric ^a	Other ^b
I	HCoV-229E	Human	X upper		
	TGEV	Pig	X upper	X S1	
	PRCV	Pig	X upper/lung		Viremia
	PEDV	Pig		X SL, colon	
	FIPV	Cat	X upper	X	Systemic
	FCoV	Cat		X S1	
	CCOV	Dog		X S1	
	RaCoV	Rabbit			Systemic
II	HCoV-OC43	Human	X upper	?? (BCoV?)	
	NUN	Mouse		X	Hepatitis, CNS, systemic
	RCoV (sialodocryadenitis)	Rat	X		Eye, salivary glands
	BEV BCoV	Pig Cattle	X X upper/lung	X S1, colon	CNS
III	IBV	Chicken	X upper	X	Kidney, oviduct
	TCoV (TECoV)	Turkey		X S1	
IV??	SARS	Human	X lung	X (?)	Viremia, kidney?
IIA?	Civet cat CoV	Himalayan palm civet	X	X	Subclinical?
		Raccoon dog			
	Raccoon Cat CoV		?	X	Subclinical?

Key: a S1 = small intestine; ?? = BCoV-like CoV from a child, ? = unknown. b CNS = central nervous system.

This narrative has changed since the outbreak of SARS and MERS epidemics in 2003 and 2012 respectively all recording high casualties at each instance by a new strain of Coronavirus.⁵⁻⁷

The SARS-COV-2 a novel coronavirus infection is said to have originated from a bush meat market in Wuhan China while theories of a laboratory accident in the same China are rife. There are also newer information laying claim to the fact that before the COVID outbreak in China, Americans had already got infected by the virus and were already spreading in the country. SARS-COV-2 has plunged the entire world into the most deadly pandemic in recent times since the Spanish Flu of 1918. As at 24th April, 2020, the global infection rate stood at 2.71 million people with over 191,000 deaths. In Nigeria, over the same period the disease burden stood at 981 infections with 31 deaths.⁸⁻

¹¹Due to the rapid spread of SARS-COV-2 with high morbidity and mortality the entire world is aggressively in search for a lasting cure and prevention. This includes the most potent preventive measures including production of

vaccines, and the most appropriate drugs to treat symptomatic cases. This search has led to the trial of virtually all groups of drugs and herbs presently available to humanity in different countries and cultures all in a bid to bring the present onslaught by COVID 19 to a halt. In this review paper, we have carefully looked at the management outcomes of some of the documented drugs and herbs used to combat the raging COVID-19 pandemic¹²⁻¹⁴.

Lopinavir/Ritonavir

The lopinavir-Ritonavir combined oral tablet is used for the treatment of HIV infections by decreasing the amount of HIV particles in the body for the body immune system to work better. They are non-protease inhibitors and may cause sleeping disturbances among other gastrointestinal side effects. Its IUPAC name is: (2*S*)-*N*-[(2*S*,4*S*,5*S*)-5-[[2-(2,6-dimethylphenoxy)acetyl]amino]-4-hydroxy-1,6-diphenylhexan-2-yl]-3-methyl-2-(2-oxo-1,3-diazinan-1-yl)butanamide. Ritonavir, a potent inhibitor of cytochrome P450 3A4 enhances bioavailability of lopinavir for optimum systemic and tissue activity¹⁵.

In a randomized controlled clinical trial at Jin Yin-Tan hospital in Wuhan, Hubei Province of China, 400mg and 100mg of lopinavir were randomly given to SARS-CoV-2 infected patients. Patients were monitored from day 0 to 28 until discharge or death. Results showed that all the 199

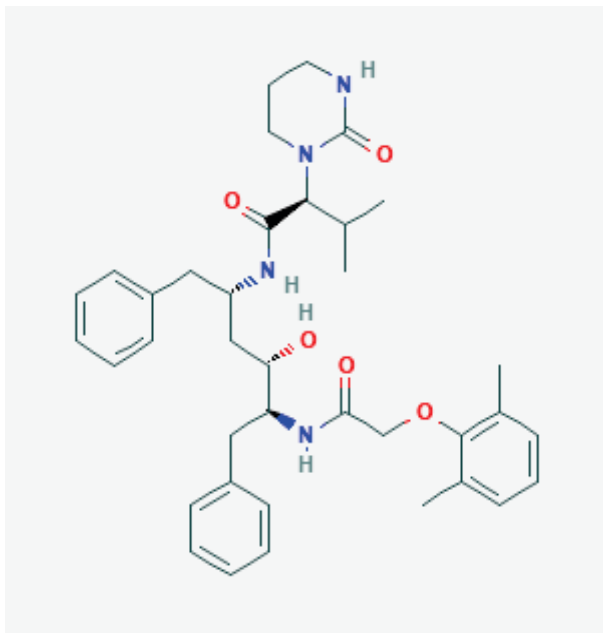
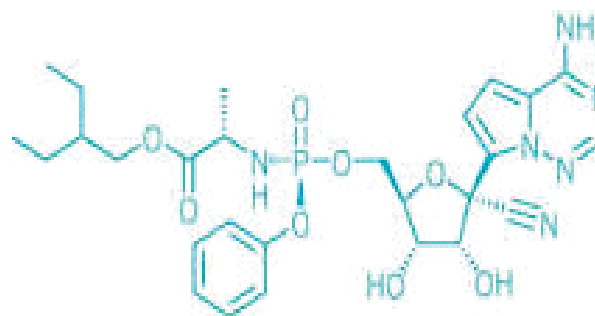


Figure 1: Structure of Lopinavir



Remdesivir

Figure 2: Structure of Remdesivir

patients followed up did not show any clinical improvement different from those on conservative symptomatic management. Trials in England, Italy USA among other countries showed similar outcomes.^{16,17}

Remdesivir and EIDD-2801

Remdesivir and EIDD-2801 are both nucleoside analogues that metabolize into an active form that blocks RNA polymerase which is essential for viral replication. While EIDD-2801 can be given in pill form, remdesivir can only be given intravenously. Its IUPAC name is 2-ethylbutyl (2S)-2-[(2R,3S,4R,5R)-5-(4-aminopyrrolo[2,1-f][1,2,4]triazin-7-yl)-5-cyano-3,4-dihydroxyoxolan-2-yl]methoxy-phenoxyphosphoryl]amino]propanoate and was also found to be effective in the treatment of MERS-CoV infections¹⁸

In a study carried out on 61 SARS-CoV-2 infected patients on remdesivir clinical trial; the patients were selected as follows: United States (22 patients), Japan (9), Italy (12), Austria (1), France (4), Germany (2), Netherlands (1), Spain (1), and Canada (1). A total of 40 patients (75%) were men with the age range of 23 to 82 years. Thirteen of the patients died by the completion of the treatment while

at least 50% of the patients presented with various complications. EIDD-2801 with its similarity to remdesivir showed a better trial on apes of *Macaca* species infected with SARS-CoV-2 and is being awaited for license from American FDA for human trial.^{19,20}

Oseltamivir and Zanamivir (Neuraminidase Inhibitors)

These drugs inhibit neuraminidase enzyme expressed on viral surfaces. The enzyme helps in promoting viral release from infected cells and also facilitates viral movements within the respiratory tract. Oseltamivir has the generic name of (3R,4R,5S)-4-acetylamino-5-amino-3-(1-ethylpropoxy)-1-cyclohexene-1-carboxylic acid, ethyl ester, phosphate. The drugs are useful in the management of influenza and flu-like infections and were tried in Wuhan China at the onset of COVID-19 pandemic but both showed no encouraging outcomes.²¹

Peptide Inhibitors

Computer simulations are being carried out to find the four peptides that mimic the virus-binding domain of the human protein that allows SARS-CoV-2 to enter cells. To infect a cell, SARS-CoV-2 uses its spike protein to attach to the ACE2 receptor on surfaces of certain human cells. This attachment enables the virus to fuse with the host cell membrane and gain entry. Researches are currently ongoing to find compounds that block key regions of the spike protein and then preventing the virus from infecting human cells. In a study carried out on EK1CA, it was found to be highly effective against membrane fusion and infection of other human coronavirus, pseudovirus tested including SARS-CoV, MERS-CoV, and SARSr-CoVs. It also potentially inhibited the replication of 5 live human coronaviruses examined including SARS-CoV-2. It was also observed that intra-nasal application of EK1C4 before or after challenge HCoV-OC43 protected mice from infection. This suggests that EK1C4 could be used for prevention and treatment of infection caused by SARS-CoV-2 emerging and re-emerging coronaviruses.^{22,23}

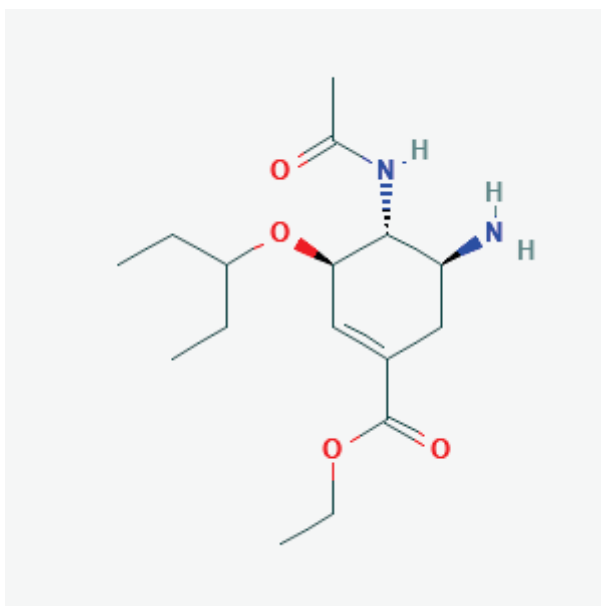


Figure 3: Structure of Oseltamivir

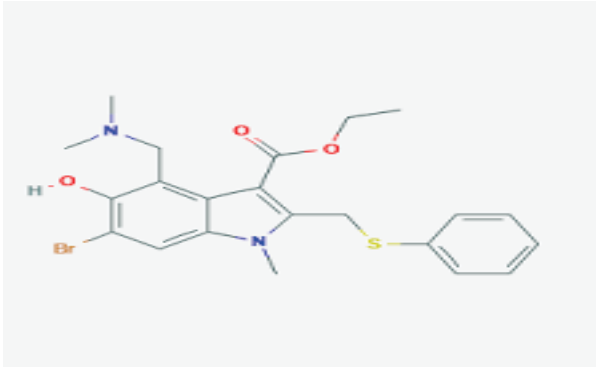


Figure 4: Structure of Arbidol

Arbidol (Umefenovir)

Arbidol (Etyl 6-bromo-4-[(dimethylamino)methyl]-5-hydroxy-1-methyl-2-[(phenylsulfanyl)methyl]-1-H-indole-3-carboxylate) is a broad-spectrum antiviral drug that inhibits cell entry of enveloped viruses by blocking viral fusion with host cell membrane. It interacts with the polar head-group of phospholipid at the membrane interface hence blocking inhibiting the early stages of viral entry into host cells. This Soviet drug for treatment of influenza in both adults and children was tried for treatment of COVID-19 in China but there were no encouraging outcomes²⁴.

Lamivudine (2(1H)-Pyrimidinone, 4-amino-1-[2-(hydroxymethyl)-1,3-oxathiolan-5-yl], (-)(2R,5S) 2',3'-Dideoxy-3'-thiacytidine) and Tenofovir- bis (isopropylxycarbonyloxymethyl) ester are nucleoside

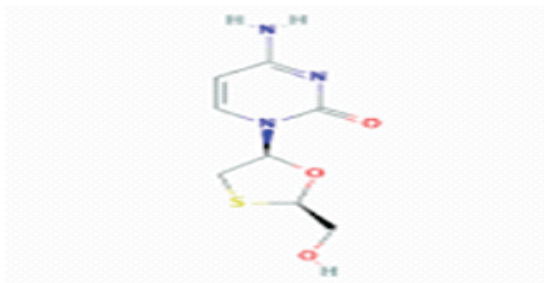


Figure 5: Structure of Lamivudine

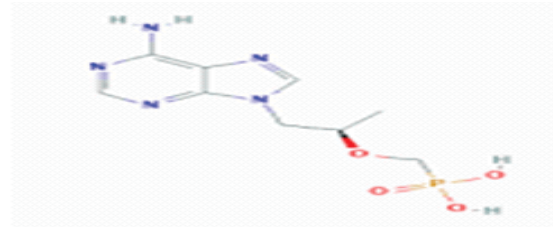


Figure 6: Structure of Tenofovir

reverse transcriptase inhibitors that block the HIV enzyme called reverse transcriptase. This prevents HIV from multiplying thus reducing HIV particles in the body. The drug is used for treatment of HIV/AIDS in both adults and children in combination with nevirapine and stavudine.

Lamivudine is a potent drug for the treatment of chronic hepatitis B infection and is readily available and affordable. These drugs have been tried in China, Singapore and South Korea but without encouraging results^{25,26}.

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDs are those medications that relieve or reduce pain and hence are also referred to as non-opioid analgesics. The commonest NSAIDs in common use are aspirin, naproxen sodium and ibuprofen. Prescription NSAIDs include oxaprozin, etodolac, indomethacin, naproxen, nabumetone, diclofenac and vimovo. They are useful in the treatment of headache, neck pains, backache, cancer pain and neuropathic pain. NSAIDs act by blocking the enzyme cyclooxygenase that is useful in the production of prostaglandins that are essential in inflammation. Reducing the amounts of prostaglandins that are produced as a result of tissue injury then reduces inflammation and pain. NSAIDs also reduce high temperature and fever. Studies from China, most parts of Asia and Europe have not given any convincing results to conclude that NSAIDs help reduce the progression of SARS-CoV-2 infection. Indomethacin however was found to reduce COVID-19 progression in some cases.²⁷⁻²⁹

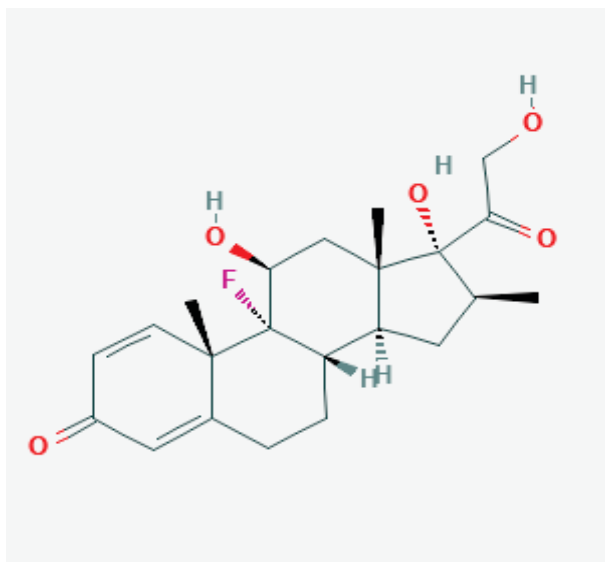
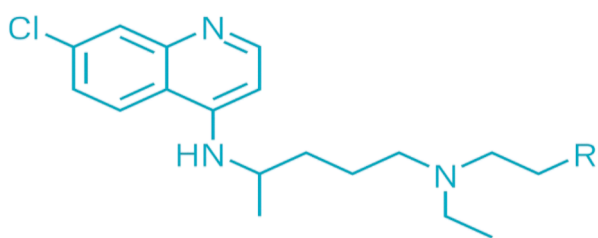


Figure 7: Structure of Betamethasone

Steroids

Steroids are man-made version of chemicals that are referred to as hormones which are made naturally in the human body. Steroids are designed to act like these hormones to reduce inflammation. There are two types of steroids- the catabolic also referred to as corticosteroids, and anabolic used by body builders and athletics. Corticosteroids can generally be grouped into short acting- cortisone, hydrocortisone and deflazacort; intermediate acting- prednisone, prednisolone, methylprednisolone;



Chloroquine, R = H
Hydroxychloroquine, R = OH

Figure 8: Chloroquine and Hydroxychloroquine Structure

and long acting- dexamethasone and betamethasone. Steroids are generally used in the treatment of clinical conditions such as rheumatoid arthritis, lupus, gout, inflammatory arthritis, auto-immune conditions, uveitis and psoriatic arthritis.^{30,31}

In an observational study carried out in Wuhu, Anhui province of China on 31 patients with SARS-CoV-2 infection and treated with corticosteroids, there was no association between corticosteroid treatment and virus clearance time. It is however not certain whether a much larger sample size with racial and geographical variations could influence this study outcome.³²

Chloroquine, Hydroxychloroquine

Chloroquine [4-*N*-(7-chloroquinolin-4-yl)-1-*N*,1-*N*-diethylpentane-1,4-diamine;phosphoric acid] is an aminoquinolone that was first synthesized in Germany by Bayer in 1934 primarily for the treatment of malaria until the development of resistance four decades later. It was granted FDA approval in October, 1949. Chloroquine and its derivative hydroxychloroquine has been replaced by pyrimethamine, artemisin, and mefloquine in the treatment of malaria. The drug is however still useful in the treatment of other clinical conditions such as HIV, systemic lupus erythematosus (SLE) and rheumatoid arthritis. Chloroquine acts by inhibiting the formation of hemozoin (Hz) from the heme released by the digestion of haemoglobin. The free heme then lyses membranes and leads to parasite death.³³

In a review study carried out by Cartegiani et al in Italy and Israel, they looked at a narrative letter, one in-vitro study, one editorial expert consensus paper, two national guidelines documents, and 23 ongoing clinical trials in China on use of chloroquine and hydroxychloroquine on SARS-CoV-2 patients. The authors found out that chloroquine and hydroxychloroquine were effective in limiting the replication of SARS-CoV-2 in vitro. Also Devaux et al in France found out that there were encouraging results from preliminary trials of chloroquine on SARS-CoV-2 infected patients in China. These research findings could largely have influenced the

decision of President Donald Trump of United States of America to publicly declare that chloroquine and hydroxychloroquine should be given to all COVID 19 patients in America. This decision has been strongly opposed by leading health professionals in USA including Dr Anthony Fauci, head of the US National Institute of Allergy and Infectious Diseases. The American medical experts have cited lack of sufficient scientific proof to support the efficacy of chloroquine and hydroxychloroquine on successful treatment of COVID 19 patients.^{34,35}

Azithromycin

Azithromycin [(2*R*,3*S*,4*R*,5*R*,8*R*,10*R*,11*R*,12*S*,13*S*,14*R*)-11-[(2*S*,3*R*,4*S*,6*R*)-4-(dimethylamino)-3-hydroxy-6-methyloxan-2-yl]oxy-2-ethyl-3,4,10-trihydroxy-13-[(2*R*,4*R*,5*S*,6*S*)-5-hydroxy-4-methoxy-4,6-dimethyloxan-2-yl]oxy-3,5,6,8,10,12,14-heptamethyl-1-oxa-6-azacyclopentadecan-15-one] is a biostatic antibacterial drug that is useful for the treatment of various bacterial infections in the body including respiratory, skin, ear, eye, and sexually transmitted infections. It acts by inhibiting bacterial growth by binding to the 50s ribosomal subunit of bacteria, thus inhibiting translation of mRNA nucleic acid synthesis in bacteria. This azalide derived from

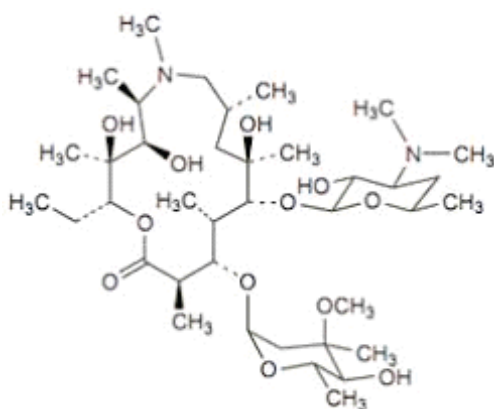


Figure 9 : Azithromycin Structure

erythromycin, a member of subclass of macrolide antibiotics goes by several trade names including zithromax, zmax, azitrom, goxil and azenil is excreted by the biliary and kidney routes in small amounts (4.5%).

In a study carried out in France on 36 SARS-CoV-2 infected patients of which 6 were asymptomatic, 22 had upper respiratory tract infection, and 8 had lower respiratory tract infections. Twenty of the patients were placed on 600mg of hydroxychloroquine plus azithromycin and were monitored from day one to six. There was much significant viral reduction at day 6 compared to the controls. In another similar study in France on 80 mildly infected COVID 19 patients, a combination of hydroxychloroquine and azithromycin were given over a period of at least 3 days. All patients were found to improve clinically with a rapid fall in nasopharyngeal viral load in 83% of the patients by day 7 and 93% at day 8. Also virus cultures from patient respiratory samples were negative in 97.5% of the them at day 5 thus shortening average duration of stay at infectious disease unit. A multi-centre study on a larger population may give a more convincing result.³⁶⁻³⁸

Chinese Herbs

Lianhuaqingwen (LH-C) and ShuFengJieDu are Chinese herbal capsule preparations which have been shown to be effective against some respiratory viruses such as influenza. In a study on viral properties of LH-C in vitro, it was found that LH-C inhibited the proliferation of influenza virus strain in vitro. There was a decrease of the viral titres in the lungs of mice studied. It was also observed

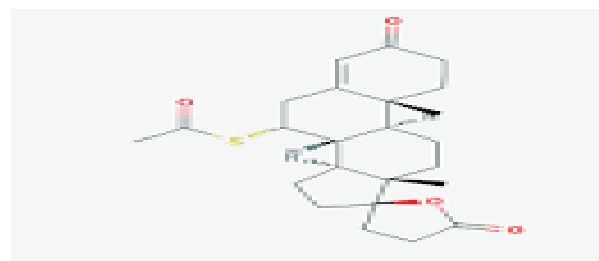


Figure 10 : Spirinolactone structure

that there was a decrease in the level of inflammatory cytokines in the early stages of infection^{39,40}.

Spironolactone

Also popularly called aldactone (7 α -Acetylthio-17 α -hydroxy-3-oxopregn-4-ene-21-carboxylic acid γ -lactone) is an aldosterone antagonist that acts primarily by competitively binding to receptors of aldosterone dependent sodium-potassium exchange site in the distal convoluted renal tubule. It is useful in the treatment of several clinical conditions such as: heart failure, hyperaldosteronism, adrenal hyperplasia, hypertension, and nephritic syndrome.

Studies have shown that hypertensives on angiotensin converting enzyme inhibitors (ACEIs) with COVID-19 disease record higher mortality and morbidity due to the use of ACEIs. This is as a result of an over-expression of ACE-2 receptors (ACE-2Rs) in the respiratory system of COVID-19 patients. It is therefore believed that spironolactone could reduce ACE-2 expression on lung-cell surfaces. Introduction of spironolactone will then balance the sudden withdrawal effects of ACEIs and angiotensin receptor blockers hence reducing the high mortality and morbidity among hypertensives infected with SARS-CoV-2. This drug has been tried but at this stage there is not yet desired results.^{41,42}

Angiotensin Converting Enzyme Inhibitors (ACEIs)

SARS-CoV-2 enters cells through angiotensin II converting enzyme (ACE-II). ACE-II expression increases in patients treated with drugs inhibiting the enzyme or with angiotensin II receptor blockers (AT II-RBs). ACE inhibitors include enalapril, ramipril, captopril, lisinopril, and AT II-RBs include losartan, candesartan, valsartan, iversatan, and termisatan. An abrupt withdrawal of these drugs in the course of COVID-19 management could pose serious risks and hence should be properly substituted. Also, their continued use in SARS-CoV-2 infected patients add no value to the disease management and in fact have shown to cause more harm than good⁴³⁻⁴⁵.

Vitamins and Minerals

The vitamins that have been tried against SARS-CoV-19 include vitamins A, B, C, D and E, and minerals include iron, selenium and zinc. The macro- and micro-nutrients are believed to strengthen immunity and help prevent SARS-CoV-2 infections or reduce the impacts of the infections in the body. Vitamin A helps in maintaining structure of cells in the epithelial linings of skin, respiratory and gastrointestinal tracts. It forms a barrier and strengthens the first line of defense and is useful in synthesis of antibodies that neutralize pathogens. The B group of vitamins, B6, B9 and B12 contribute to the body's first immune response on recognition of a pathogen by effecting the production and activity of Natural Killer (NK) Cells. The NK cells act by causing infected cells to undergo apoptosis. Vitamin C and E help in mopping up free radicals in the body from oxidative stress of cells. This prevents accumulation of toxic elements from cellular activity hence preventing cell death and fatigue^{46,47}.

Iron, Zinc and Selenium

These metals help in the healthy development of immune cells. Iron helps to increase the number of free radicals in tissues that destroy pathogens. It also regulates and strengthens antigen recognition and presentation. Zinc and Selenium play the role of antioxidant by mopping up

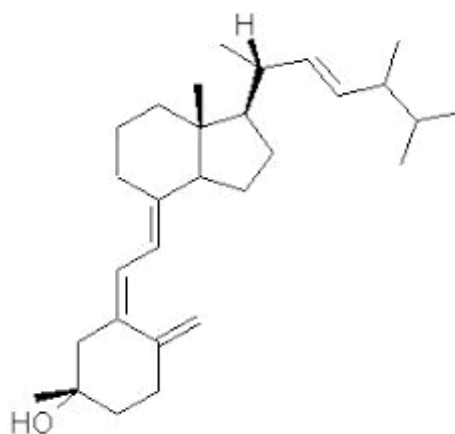


Figure 11 : Structure of Vitamin D

excess free radicals and hence healing the damages caused by oxidative stress, and preserving and maintaining integrity of skin and mucous membranes⁴⁷⁻⁴⁸.

Calciferol (Vitamin D)

Vitamin D is a group of fat soluble secosteroids that is responsible for the intestinal absorption of calcium, magnesium, phosphate and several other functions. It is commonly found in fish liver oils, salt water fish, milk butter, cheese, margarine and cream among other animal products. Vitamin D is converted to 25-Hydroxycholecalciferol and calcidiol by the liver and is then metabolized by the kidney into several active forms including 1,25-Dihydroxycholecalciferol and calcitriol. These active vitamin D metabolites exercise several functions in the body but principally in the maintenance of optimum blood levels of calcium and phosphorus.

Vitamin D is required by cells to help destroy pathogens. In a study carried out in San Francisco on Vitamin D and its ability to reduce respiratory tract infections including COVID-19, it was observed that: Vitamin D can induce cathelicidins and defensins that can lower viral replication rates. This will also lead to reduction in concentration of pro-inflammatory cytokines that produce inflammation that injure the lung lining causing pneumonia. Vitamin D also increases concentration of anti-inflammatory cytokines. There are however mixed results on level of effectiveness of vitamin D in the treatment of COVID-19. The only strong point for vitamin D against COVID-19 as it has so far been established is that, the outbreak occurred in the winter, a time when 25-hydroxy-vitamin D concentrations are lowest in the body⁴⁹⁻⁵¹.

Anticancer Drugs and Immune Modulators

Anticancer drugs are generally grouped into alkylating agents such as cisplatin, carboplatin and oxaliplatin; antimetabolites such as vincristine, vinblastine, docetaxel; and miscellaneous such as hydroxyurea, L-asparaginase and tretinoin. Cytotoxic drugs generally act by inhibiting the multiplication and growth of malignant cells in the body. The effect of cytotoxic drugs on SARS-CoV-2 in

London showed that cytotoxic chemotherapy specifically inhibits severe acute respiratory syndrome coronavirus in vitro. The study further found out that low dose prednisolone may have beneficial effect on COVID-19 patients. Also low doses of anticancer drugs such as methotrexate did not improve healing of COVID-19 patients. Furthermore, the study did not find any evidence that Janus Kinase (JAK) inhibitor and anti-TNF α agents are contraindicated in treatment of COVID-19 patients. Studies on other groups of drugs listed below were carried out such as: Any tumour necrosis factor (TNF) blocker, Mycophenolate, Tacrolimus, Anti-CD20, and CTLA4-Ig. None of them showed good results against COVID-19 treatment⁵²⁻⁵⁴.

Cytokine Antagonists (Tocilizumab)

Cytokines are chemical mediators of inflammation released principally by macrophages and lymphocytes during tissue injury. When released and their concentrations are within physiological limits, they help control infections and limit tissue injury but when released in excess they turn their attack against host tissues. In SARS-CoV-2 induced pneumonia there is marked hyperactivation of effector T cells with excessive production of inflammatory cytokines particularly IL-6 but also appreciable levels of IL-1, TNF Interferon gamma. This scenario is called cytokine storm and it contributes to the pathological process that leads to plasma leakage, vascular permeability, pulmonary microvascular coagulopathy and systemic disseminated intravascular coagulation. These events further disseminate SARS-CoV-2 in the body with more aggressive systemic and multiorgan damages principally, the heart, kidney and liver^{55,56}.

Administration of blocker of IL-6 (tocilizumab), anti-TNFs (infliximab, adalimumab, and IL-12 and IL-23 blockers (ustekinumab) would suppress the acute autoimmune cytokine-mediated tissue injury. These immunomodulators have been effective in the management of auto-immune disease such as rheumatoid arthritis, psoriasis, psoriatic arthritis, ankylosing

spondylitis, and inflammatory bowel diseases^{57,58}.

In a clinical trial of tocilizumab on 21 critical ill patients in ICU in Wuhan China and another critically ill in an ICU in Paris France recorded instantaneous improvement from all of them. Though the trial is on very few patients it particularly holds the promise for SARS-CoV-2 infection treatment if large scale clinical trials prove successful^{59,60}.

Convalescent Plasma

Blood plasma is a yellowish liquid component of blood that holds blood cells in circulation as the liquid part of the blood in which cells, proteins and other components are suspended. It is the intravascular fluid which makes up about 55% of the body's total blood volume. Convalescent plasma is plasma recovered from a patient that has recovered from a particular disease. When administered this plasma can give passive immunization to the recipients as a result of the presence of specific antibodies against the causative agent. Convalescent plasma has been used to treat influenza as far back as 1918 H1N1 pandemic. Also in 2003 convalescent plasma was useful in the management of SARS-CoV-1 outbreak in Hong Kong. In the present pandemic of COVID-19 in a study, 5 critically ill patients received convalescent plasma containing SARS-CoV-2 antibodies (titre >1:1000) and neutralizing antibody (titre >1:40) between day 10 and 22 of admission. The study found a significant resolution in respiratory distress of 4 out of five of the patients also with normalization of the temperature. In another study on 10 COVID-19 patients administered with convalescent plasma, all improved dramatically by day 3 post-transfusion. They all reported increase in neutralising antibody titre, oxygen saturation and lymphocyte counts. Also there was a decrease in C-reactive protein, SARS-CoV-2 viral load, and improved lung lesions on radiological examination. Yet in another study on 4 COVID-19 patients placed on convalescent plasma therapy, all the four fully recovered.

The relatively small samples in all the studies, appropriate inferences cannot be drawn as to effectiveness or otherwise of convalescent plasma in the management of SARS-CoV-

2 severe infections. Studies on a much larger sample size is therefore needed⁶¹⁻⁶⁵.

Antidiabetic Drugs (Biguanides)

The antidiabetic drugs that appear to have antiviral properties belong to the biguanide group including buformin, phenformin, and metformin. These drugs were found effective in the treatment of the 1971 influenza outbreak. It was found that diabetic patients who were treated with phenformin and buformin had far less incidence of influenza than those treated with sulfonylureas or insulin. Studies have also shown that both buformin and phenformin reduce the mortality of influenza in mice. The authors therefore recommended that buformin and phenformin inhalation should be considered a treatment strategy for influenza disease. Biguanides have proved to be effective against SARS-CoV and MERS-CoV and by extension could hold promise against the novel SARS-CoV-2 infections. More exploration may be required to ascertain this⁶⁶⁻⁶⁹.

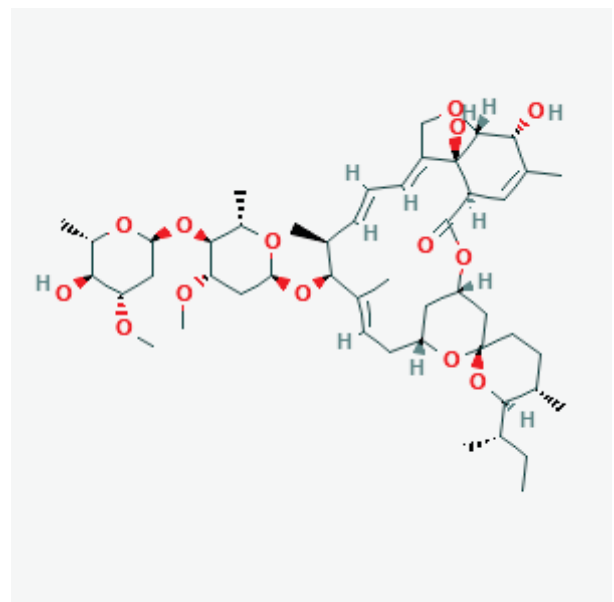


Figure 12 : Structure of Ivermectin

Ivermectin (Antiparasitic Drug)

Ivermectin is broad spectrum antiparasitic drug that is mainly used to treat roundworms. It can be used against several parasitic infections including strongyloidiasis, onchocerciasis, pediculosis capitis, blepharitis, Mansonella ozzardi filariasis, Mansonella streptocerca filariasis, scabies and gnathostomiasis. It acts by causing an influx of chloride ions through the cell membrane of invertebrates through activation of specific ivermectin-sensitive ion channels. This causes hyper-polarisation leading to muscle paralysis and death of parasites.

In a study carried out in Australia where ivermectin was treated with SARS-CoV-2 infected Vero/hSLAM cell lines, and the supernatant and cell pellets were harvested at days 0-3. This was analysed by RT-PCR for replication of SARS-CoV-2 RNA. It was observed at 24 hours there was a 93% reduction in viral RNA present in the supernatant. And by 48 hours there was a 5000-fold reduction in viral RNA in ivermectin-treated cell culture media compared to the control. In a study in Pennsylvania USA by Guzzo, attaining optimum tissue antiviral levels even with extremely high dosages without toxic consequences in

vivo appeared to be one major draw back in exploring this drug for COVID-19 treatment⁷⁰⁻⁷².

Research into enhancing optimum tissue availability of ivermectin at much lower doses may be required to adequately explore its SARS-CoV antiviral potentials^{73,74}.

Heparin

Heparin (2S,3S,4R,5R,6R)-6-[[[(2S,3S,4S,5R,6S)-6-[[[(2R,3S,4S,5R)-2-carboxy-4,6-dihydroxy-5-(sulfooxy)oxan-3-yl]oxy]-2-hydroxy-4-(sulfomethyl)-5-(sulfooxy)oxan-3-yl]oxy]-3-[[[(2R,3R,4R,5S,6R)-3-acetamido-4,5-dihydroxy-6-[(sulfooxy)methyl]oxan-2-yl]oxy]-4,5-dihydroxyoxane-2-carboxylic acid) is an anticoagulant that helps prevent formation of blood clots and it can be used before surgery to reduce the risk of blood clot formation. It acts by binding to the enzyme inhibitor antithrombin III causing a conformational change that result in its activation through an increase in the flexibility of its reactive site loop. The activated antithrombin then inactivates thrombin, factor Xa along with other proteases, thus preventing and dissolving blood clots.

A study was carried out on 499 COVID-19 patients with pneumonia at Tongji hospital in Wuhan China who were treated with heparin and another 104 non-COVID pneumonia patients. A 28 day follow up showed that the heparin users had lower mortality compared to those who did not use heparin. It was also observed that patients with SARS-CoV-2 associated pneumonia had lower platelet counts compared to the control.⁷⁵

In another study in the same hospital, 499 patients with severe COVID-19 were consecutively enrolled and 99 of them placed on low molecular heparin for 7 days or longer. No difference was found in the 28-day mortality between heparin users and non-users. The mortality of heparin users was however found to be lower than that of non-users in patients with sepsis-induced coagulopathy or D-dimer of > 6-fold of upper limit. More research is therefore required to establish the actual position of heparin in the treatment of severe SARS-CoV-2 infections⁷⁶⁻⁷⁸.

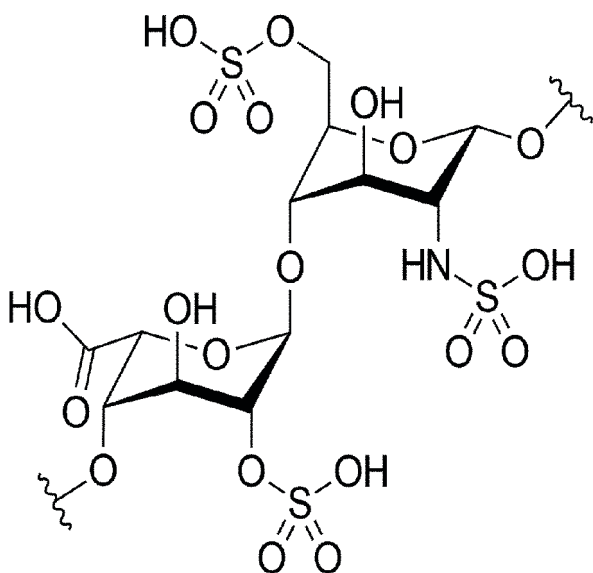


Figure 13: Heparin Structure

COVID Organics

COVID Organics is a herbal preparation prepared by Malagasy Institute of Applied Research of Madagascar. The herb is an extract from *Artemisia annua* which is a plant of Chinese origin and since the 1970s it is being used for the treatment of malaria. The drug is believed to have played a significant role in the SARS-CoV-2 morbidity and with no mortality recorded in the country with over 92 persons out of 128 infected successfully treated. The WHO is yet to accept the preliminary report from Madagascar about the herb and therefore more research is required to establish the veracity or otherwise of the claims and of its safety and tolerability profile in adults and children⁷⁹⁻⁸².

Magic Foods

There are general traditional beliefs among Africans and beyond that ingestion of certain foods could cure COVID-19. These categories of food include garlic, ginger, lemon, supposedly alkaline foods such as limes, oranges, turmeric tea and avocados. These supposedly alkaline foods are believed to have a pH in the range of 9.9 higher than the optimum growth pH for SARS-CoV-2 and hence capable of killing the viruses. But ironically these foods and substances are mostly acidic in nature and some with pH below 3. Also ketogenic diets high in fat and low in carbohydrates is believed to inhibit the multiplication of SARS-CoV-2 in the body. While taking of balanced diet rich in minerals, proteins, fats and carbohydrates is needed for a general boosting of the body's immunity, the specific antiviral properties of these foods against SARS-CoV-2 cannot be ascertained. As a matter of fact they have not healed any COVID-19 patient anywhere in the world⁸³⁻⁸⁵.

Alcohol

The active ingredient in alcohol is ethyl alcohol which is present in all alcoholic beverages be it wine, beer, spirits, or other mixtures depending on its percentage content and other additives. Alcohol has both short and long term effects on the body and can gradually attack every organ system in the body with gradual weakening of the immune system. It is said to facilitate the development of some

cancers and alters the thoughts, judgement, decision making and behavior of an individual. There are general myths surrounding alcohol consumption in the midst of the ongoing COVID-19 pandemic. These include: consuming alcohol destroys the causative agent SARS-CoV-2 and that drinking strong alcohol kills the virus in the inhaled air; also alcohol stimulates and strengthens immunity of an individual against COVID-19. All these assertions have no scientific basis and are perhaps on the contrary in the midst of prolonged intake of alcohol under the ongoing COVID-19 pandemic. Cutting down on alcohol consumption and outright stoppage will rather reduce the rate of infection and as well as the degree of severity of infections⁸⁶⁻⁸⁹.

Disinfectants

Disinfectants are chemical agents applied to non-living objects in order to destroy bacteria, viruses, fungi, mold or mildews living on the objects. Disinfectants are generally grouped into: quaternary ammonium compounds, chlorine compounds, alcohols, aldehydes, iodophors, phenolic compounds and hydrogen peroxide. Disinfectants come in various forms such as gaseous sprays, Liquids, hand sanitizers, soaps among others. Gaseous disinfectants include formaldehyde, ethylene oxide and propylene oxide among others while hand sanitizers are either alcohol-based or alcohol-free⁹⁰.

Alcohol-based contain 60-95% alcohol in form of ethanol, isopropanol or n-propanol where alcohol immediately denatures proteins killing microorganisms. Alcohol-free products include benzalkonium chloride or antimicrobial agents such as triclosan. Since the onset of COVID-19 pandemic there has been a sustained use of disinfectants especially sprays and hand sanitizers by the public. Studies have shown that outdoor spraying of disinfectants does not achieve any meaningful benefits against eradication of SARS-CoV-2 as the disinfectant is inactivated by dirt and debris^{90,91}.

According to WHO, streets and pavements are not considered as reservoirs of COVID-19 infection while regular hand washing with soap and use of hand sanitizers is beneficial. Excessive use of hand sanitizers to prevent

COVID-19 however could predispose to the following:

I. It could trigger irritation of skin making it more vulnerable to further destruction.

ii. It makes the skin excessively dry turning it into a hotbed of disease bacteria increasing the risk of viral infection including SARS-CoV-2 through cuts in the skin.

Thorough hand washing using soap for 30 seconds provides effective protection against COVID-19 and other infections. The outcry in USA over suggestion from President Donald Trump to test efficacy of disinfectants by injecting them into COVID19 patients is justifiable. Disinfectants as generally known are only meant for topical and external use and injecting them into COVID-19 patients could kill the person faster than the disease itself due to their corrosive nature^{92,93}.

CONCLUSION

This is not the complete list of drugs being tried for COVID-19 across the globe as there are other drugs as much as 70 plus currently being experimented and none of these drugs so far has offered a solution to the effective treatment of COVID-19. Due to the fact that the disease literally ambushed humanity and took the world by surprise, the scientific world does not have the luxury of time to carry out a well-planned and structured study over considerable period of time with large sample sizes concerning all the drugs listed in this review. This makes both the successful and failed drugs difficult to adopt in policy formulation on the fight against the disease for now. Moreover, concerning the deadly nature of the disease, ethical and moral constraints abound restraining using sick people who may have benefited from a treatment trial as control subjects.

Recommendations

It is difficult to recommend any line of treatment without sufficient scientific evidence for now. High-impact treatment options for COVID-19 so far are; Antiviral drugs, Anti-inflammatory drugs, ACE inhibitors and angiotensin receptor blockers, Hydroxychloroquine + Azithromycin

and convalescent serum among several other options including COVID organics. We however recommend that treating Physicians are at liberty to use appropriate combination of medications at their disposal based on information provided above. These drugs may possibly reduce the rates of progressions into severe disease requiring intensive care and ventilators as more efforts to find lasting cure should be intensified.

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Declaration

We declare no conflict of interest.

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