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IMPLEMENTATION OF FUNCTIONAL GROUP ANALYSIS OF DRUGS FOR COVID-19

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Abstract

The severe acute respiratory syndrome Corona Virus also known as COVID-19 has become the current health issue to the entire world to suppress the disease precautionary measures is the only method which stops person to person transmission till effective method of treatment vaccine is developed. Drug repurposing is the concept of identifying therapeutically potent molecule from the library of preexisting molecules in the present paper few drugs are selected and impact of it on COVID-19 drugs containing ethanolamine/propylamine fragments along with heterocycles have some potential anti-viral results. Similarly, there is the possibility of controlling the COVID-19 infection by nucleotide analogues. Here we also highlight some drugs and its advantages and disadvantages. Patients' data is analyzed with the help of statistically tool i.e., regression and correlation methods. The Drug repurposing approach provide an In Site about the therapeutics that might be helpful in treating corona virus disease.

Introduction

Novel Corona Virus disease (COVID-19) has become a plague threat to public health. It's a respiratory disease-causing lever, fatigue, dry cough, muscle ache, shortness of breath, and in some cases, it leads up to pneumonia [1, 2].

There are four different types of Corona Viruses are there. They are α covs β covs γ covs, and δ covs among which α covs, β covs infects mammals while γ covs, and δ covs birds.

In serious conditions, it causes ARDS-acute respiratory distress syndrome

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i.e. a lung inflammation so severe that fluid builds up around and within the lungs which may cause septic shock because of a dramatic fall in blood pressure and body orangs are starved for oxygen. The period of this Corona Virus is approximately 1 to 14 days symptoms and severity vary from patient to patient. Because of the weak immune system, elderly people, pregnant women, children, people with diseases like asthma, heart problems, diabetes less low level of vitamin D, affect more.

The epicenter of the outbreak was located in Wuhan, Hubei provenience, China [2, 3]. This outbreak was declared a public health emergency of international concern on 30th January 2020 by WHO thanks to its fast transmission.

Literature Review

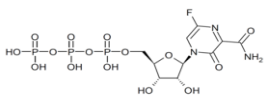
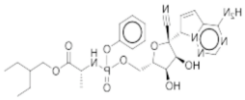
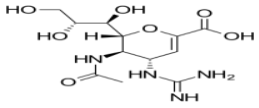
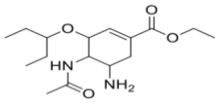
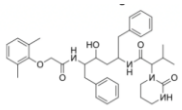
The causative agent for COVID-19 is SARS-COV-2 (Severe acute respiratory syndrome-2). Drug repositioning (also referred to as drug repurposing, reprofiling, re-tasking, or Therapeutic switching) is that the repurposing of an approved drug for the treatment of various diseases (or) medical conditions than that it was originally developed [5].

The development of drug its disposition (absorption, distribution, metabolism, and excretion known by the acronym ADME) and pharma co kinetics (the Mathematica description of the speed of their process and of concentration-time relationships), plays a central role throughout pharmaceutical research and development [7].

ADME studies provide the sole basis for critical judgments from a situation where the behavior of a drug is known to those where it's unknown. It also gives the knowledge for a full understanding of the mechanism of action and toxicity. (ncbi.nlm.nih.gov/books).

There is a computational database for genome study that's useful in fast-track drug discovery other research directions include the event of a COVID-19 vaccine [8] and convalescent plasma trans-fusion [9].

Table 1. List of medicine used for the treatment of COVID-19 [10].

No	Name	Structure	Active against	Mechanism
1	Favipiravir		Influenza	Inhibits viral RNA-dependent RNA polymerase (RdRp)
2	Remdesivir		Ebola virus Respiratory syncytial virus	Viral RNA polymerase
3	Zanamivir		Influenza viruses	Neuraminidase inhibitor
4	Oseltamivir		Influenza virues A	Inhibits the neuraminidase enzyme
5	Lopinavir		HIV	Protease inhibitor

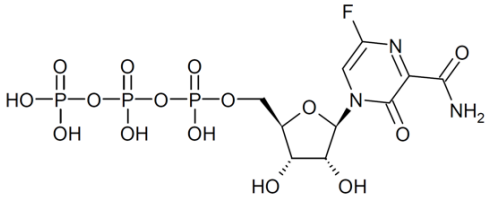
Molecular docking. Molecular docking could be a structure-based drug design approach to stop the essential aminoalkanoic acid interaction between the chosen protein and generated ligands with low energy conformation [11].

Methodologies. During this present paper information regarding COVID-19 source data is maintained by Hannah Ritchie and was downloaded directly from Corona Virus Source data. A statistical tool Regression and Correlation methods wont to analyze the info. Unfortunately, no medicine or anti-virus vaccine has yet been officially approved to treat COVID-19-associated pathologies.

At present clinical management includes infection prevention, control measures, and supportive care including supplementary oxygen and mechanical ventilation when indicated. While many countries are working toward a vaccine against SARS-CoV-2, it's almost certain that there'll be no vaccine available before the tip of this year [12].

Several drugs are identified supported their differing modes of action on the virus and various pathways it traverses, including several antivirals (lopinavir/ritonavir combination, remdesivir, and favipiravir); two antimalarials (chloroquine and hydroxychloroquine); ACE2 inhibitor (losartan); immunosuppressive agents (tocilizumab, leronlimab and corticosteroids); TMPRSS2 inhibitor (camostat mesylate); anti-parasitic drugs (ivermectin and nitazoxanide); a gold-containing drug, auranofin, an immunomodulator utilized in sepsis and leprosy (Sepsivac, mycobacterium w heat-killed injections); allogeneic Placental expanded (PLX) cells; and convalescent plasma [13].

Drugs Details. Sold under the name Avigan among others, [17] is an antiviral medication want to treat influenza in Japan. [14] it's also being studied to treat many other viral infections. [14] just like the experimental antiviral drugs T-1105 and T-1106, it is a pyrazine carboxamide derivative.



It is being developed and made by Toyama Chemical (Fujifilm Group) and was approved for medical use in Japan in 2014. [15] In 2016, Fujifilm licensed it to Zhejiang Hisun Pharmaceutical Co. of China. [16] It became a drug in 2019, allowing the corporate to supply it within the People's Republic of China.

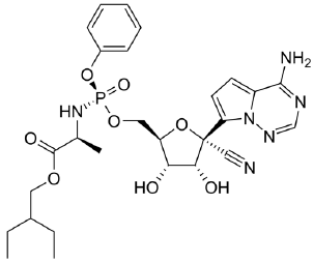
Favipiravir has been approved to treat influenza in Japan. [15] It is, however, only indicated for novel influenza (strains that cause more severe disease) instead of seasonal influenza. [15] As of 2020, the probability of resistance developing appears low. [15].

The adverse effect of Favipiravir

- Reduced weight
- Vomiting
- Reduced locomotive activity

- Decreased production of red blood cells
- An increased liver function like the assemble of aspartate aminotransferase, alkaline phosphatase, alanine aminotransferase, and total albumin.
- Increased vacuolization in hepatocytes
- It is teratogenic meaning; it can cause congenital defects and therefore should be avoided in pregnant women.

Remdesivir - Remdesivir, sold under the brand name Veklury, [18] [19] may be a broad-spectrum antiviral medication developed by the biopharmaceutical company Gilead Sciences. [20] It is administered via injection into a vein. [21] [22] Remdesivir is being tested as a treatment for COVID-19 and has been authorized for emergency use within the US, India, [8] Singapore, [24] and approved to be used in Japan, the European Union, and Australia for people with severe symptoms. [18] [19] [25] [26] [27] [28] It also received approval within the UK in May 2020; however, it had been visiting be rationed because of limited supply. [29] It should shorten the time it takes to endure the infection. [30]



The most common side effect in healthy volunteers has raised blood levels of liver enzymes (a sign of liver problems). [18] The foremost common side effect in people with COVID-19 is nausea (feeling sick). [18]

Side effects may include liver inflammation and an infusion-related reaction with nausea, low blood pressure level, and sweating. [31] It's a prodrug that's intended to permit intracellular delivery of GS-441524 monophosphate and subsequent biotransformation into GS-441524 triphosphate, a ribonucleotide analog inhibitor of viral RNA polymerase. [32]

Earlier studies found antiviral activity against several RNA viruses

including SARS coronavirus and MERS coronavirus, but it's not approved for any indication. [20] [25] Remdesivir was originally developed to treat hepatitis C [33] and was then tested against filovirus, virus disease and Marburg virus disease, but was ineffective for all of those viral infections. [20] [34].

The adverse effect of remdesivir

The most common adverse effects in studies of remdesivir for COVID-19 include respiratory failure and organ impairment, including low albumin, low potassium, low count of red blood cells, low count of platelets that help with clotting, and yellow discoloration of the skin. [35] [unreliable medical source?] Other reported side effects include gastrointestinal distress, elevated transaminase levels within the blood (liver enzymes), and infusion site reactions. [22]

Other possible side effects of remdesivir include

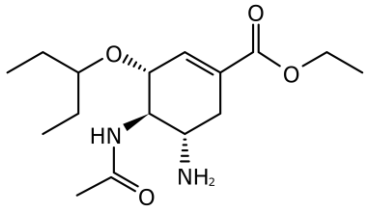
Infusion-related reactions are seen during a remdesivir infusion or around the time remdesivir was given. [36] Signs and symptoms of infusion-related reactions may include low blood pressure level, nausea, vomiting, sweating, and shivering. [36]

Increases in levels of liver enzymes, seen in abnormal liver blood tests. [36]. People that have received remdesivir, which can be an indication of inflammation or damage to cells within the liver. [36]

Oseltamivir- Oseltamivir, sold under the brand Tamiflu, is an antiviral medication wont to treat and stop influenza *A* and influenza *B* (flu). [37] Many medical organizations recommend it in those who have complications or are at high risk of complications within 48 hours of first symptoms of infection. [38] They recommend it to forestall infection in those at high risk, but not the overall population. [38] The Centers for Disease Control and Prevention (CDC) recommends that clinicians use their discretion to treat those at lower risk who present within 48 hours of first symptoms of infection. [38] [39] [40] It's taken orally, either as a pill or liquid. [37]

Recommendations regarding oseltamivir are controversial as are criticisms of the recommendations. [38] [41] [42] [43] A 2014 Cochrane Review concluded that oseltamivir doesn't reduce hospitalizations which

there's no evidence of a discount in complications of influenza. [43] Two meta-analyses have concluded that benefits in those that are otherwise healthy don't outweigh its risks. [44] [45] They also found little evidence regarding whether treatment changes the danger of hospitalization or death in high-risk populations. [44] [45] However, another meta-analysis found that oseltamivir was effective for the prevention of influenza at the individual and household levels. [46]



The adverse effect of Oseltamivir

Common side effects include vomiting, diarrhea, headache, and trouble sleeping. [37] Other side effects may include psychiatric symptoms and seizures. [37] [47] [48] within the United States, it's recommended for influenza infection during pregnancy. [56] It's been taken by a little number of pregnant women without signs of problems. [56] Dose adjustment is also needed in those with kidney problems. [37]

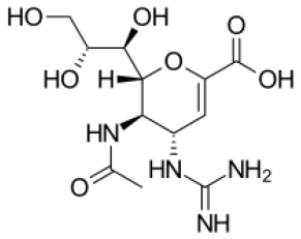
Oseltamivir was approved for medical use within the US in 1999. [37] It was the primary neuraminidase inhibitor available orally. [49] It's on the planet Health Organization's List of Essential Medicines but was downgraded to "complementary" status in 2017. [50] [51] A generic version was approved within the US in 2016. [52] [53] In 2017, it had been the 159th most typically prescribed medication within the United States, with quite three million prescriptions. [54] [55]

Common adverse drug reactions (ADRs) related to oseltamivir therapy (occurring in over 1 percent of people) include nausea and vomiting. In adults, oseltamivir increased the danger of nausea that the quantity needed to harm was 28, and for vomiting was 22. So, for each 22-adult people on oseltamivir one experienced vomiting. within the treatment of kids, oseltamivir also induced vomiting. The amount needed to harm was 19. So,

for every 19 children on oseltamivir one experienced vomiting. In prevention, there have been more headaches, kidney, and psychiatric events. Oseltamivir's effect on the center is unclear: it should reduce cardiac symptoms, but may induce serious arrhythmias. [57]

Post marketing reports include liver inflammation and elevated liver enzymes, rash, sensitivity including anaphylaxis, toxic epidermal necrolysis, abnormal heart rhythms, seizure, confusion, aggravation of diabetes, and hemorrhagic colitis, and Stevens-Johnson syndrome. [58] [51]

Zanamivir may be a medication won't to treat and stop influenza caused by influenza *A* and *B* viruses. It's a neuraminidase inhibitor and was developed by the Australian biotech firm Biota Holdings. It was licensed to Glaxo in 1990 and approved within the US in 1999, just for use as a treatment for influenza. In 2006, it was approved for the prevention of influenza *A* and *B*. [60] Zanamivir was the primary neuraminidase inhibitor commercially developed. It's currently marketed by GlaxoSmithKline under the trade name Relenza as a powder for oral inhalation.



Zanamivir is employed for the treatment of infections caused by influenza A and influenza B viruses, but in otherwise healthy individuals, benefits overall appear to be small. It decreases the chance of one's getting symptomatic, but not asymptomatic influenza. The mix of diagnostic uncertainty, the danger for virus strain resistance, possible side effects, and financial cost outweigh the tiny benefits of zanamivir for the prophylaxis and treatment of healthy individuals. [61] As of 2009, no influenza had shown any signs of resistance within the US. [62] Since then, genes expressing resistance to zanamivir were found in Chinese people infected with avian influenza A H7N9 during treatment with zanamivir. [63]

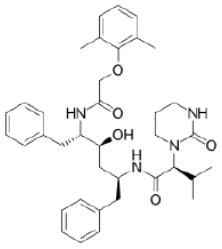
The adverse effect of Zanamivir

Dosing is restricted to the inhalation route. This restricts its usage, as treating asthmatics could induce bronchospasms. [64] In 2006 the Food and Drug Administration (FDA) found that breathing problems (bronchospasm), including deaths, were reported in some patients after the initial approval of Relenza. Most of those patients had asthma or chronic obstructive pulmonary disease. Relenza, therefore, wasn't recommended for treatment or prophylaxis of seasonal influenza in individuals with asthma or chronic obstructive pulmonary disease. [65] In 2009 the zanamivir package insert contains precautionary information regarding the chance of bronchospasm in patients with a respiratory disorder. [66] GlaxoSmithKline (GSK) and FDA notified healthcare professionals of a report of the death of a patient with influenza having received zanamivir inhalation powder, which was solubilized and administered by mechanical ventilation. [67]

In adults, there was no increased risk of reported adverse events in trials. There was little evidence of the possible harms related to the treatment of kids with zanamivir. [69] Zanamivir has not been known to cause toxic effects and has low systemic exposure to the chassis. [68]

Lopinavir is an antiviral drug class inhibitor class. It's used against HIV infections as a fixed-dose combination with another antiviral drug, ritonavir (lopinavir/ritonavir). [70]

It was patented in 1995 and approved for medical use in 2000. [71]



The adverse effect of Lopinavir

Side effects, interactions, and contraindications have only been evaluated within the drug combination lopinavir/ritonavir.

The most common adverse effects observed with lopinavir/ritonavir are diarrhea and nausea. In key clinical trials, moderate or severe diarrhea occurred in up to 27% of patients, and moderate/severe nausea in up to 16%.

[72] Other common adverse effects include abdominal pain, asthenia, headache, vomiting, and, particularly in children, rash. [72]

Raised liver enzymes and hyperlipidemia (both hypertriglyceridemia and hypercholesterolemia) are commonly observed during lopinavir/ritonavir treatment. [citation needed]

Lopinavir/ritonavir is anticipated to possess varying degrees of interaction with other medications that also are CYP3A and/or *P*-gp substrates. [73]

People with structural cardiopathy, preexisting conduction system abnormalities, ischaemic cardiovascular disease, or cardiomyopathies should use lopinavir/ritonavir with caution. [74]

On 8 March 2011 the U. S. Food and Drug Administration notified healthcare professionals of serious health problems that are reported in premature babies receiving lopinavir/ritonavir oral solution, probably due to its propanediol content. They recommend the use should be avoided in premature babies. [75]

Regression. The term 'regression' was coined by Francis Galton within the nineteenth century to explain a biological phenomenon. In rectilinear regression, a line is fitted to bivariate data. A simple regression of the shape

$$y' = a + bx$$

where b is that the parametric statistic and a is that the regression is constant. a and b are determined by the tactic of a method of least squares and y' denotes the estimated value of y. Here x is named the predictor and y is named the predictand.

Pearson Correlation. The Pearson coefficient of correlation is employed to live the strength of a linear association between two variables, where the worth $r = 1$ means an ideal correlation and therefore the value $r = -1$ means an ideal negative correlation. So, as an example, you'll use this test to search out whether people's height and weight are correlated (they are going to be - the taller people are, the heavier they're likely to be).

$$r = \frac{\sum_i (x_i - \bar{x})(y_i - \bar{y})}{\sqrt{\sum_i (x_i - \bar{x})^2}\sqrt{\sum_i (y_i - \bar{y})^2}}$$

Requirements for Pearson's coefficient of correlation

- The scale of measurement should be interval or ratio
- Variables should be approximately normally distributed
- The association should be linear
- There should be no outliers within the data
- Equation

ANALYSIS OF VARIANCE (ANOVA).

Central to the making of statistical inference within the regression setting is that the estimation of the variance from the sample residuals. Once we fit an equation, we estimate two parameters a and b. Therefore, the degrees of freedom for a sample of n data points are $(n-2)$. The variance of residuals become.

$$S_e^2 = \frac{1}{n-2}\sum_{i=1}^{n} e_i^2$$

The COVID data from June 01, 2020, to July 10, 2020, is considered.

Date	Location	New cases	New Deaths	Total Cases	Total Deaths	Weekly Cases
6/1/20	India	8392	230	190535	5394	51690
6/2/20	India	8171	204	198706	5598	53326
6/3/20	India	8909	217	207615	5815	55848
6/4/20	India	9304	260	216919	6075	58586
6/5/20	India	9851	273	226770	6348	60971
6/6/20	India	9887	294	236657	6642	62894
6/7/20	India	9971	287	246628	6929	64485
6/8/20	India	9983	206	256611	7135	66076
6/9/20	India	9987	331	266598	7466	67892

6/10/20	India	9985	279	276583	7745	68968
6/11/20	India	9996	357	286579	8102	69660
6/12/20	India	10956	396	297535	8498	70765
6/13/20	India	11458	386	308993	8884	72336
6/14/20	India	11929	311	320922	9195	74294
6/15/20	India	11502	325	332424	9520	75813
6/16/20	India	10667	380	343091	9900	76493
6/17/20	India	10974	2003	354065	11903	77482
6/18/20	India	12881	334	366946	12237	80367
6/19/20	India	13586	336	380532	12573	82997
6/20/20	India	14516	375	395048	12948	86055
6/21/20	India	15413	306	410461	13254	89539
6/22/20	India	14821	445	425282	13699	92858
6/23/20	India	14933	312	440215	14011	97124
6/24/20	India	15968	465	456183	14476	102118
6/25/20	India	16922	418	473105	14894	106159
6/26/20	India	17296	407	490401	15301	109869
6/27/20	India	18552	384	508953	15685	113905
6/28/20	India	19906	410	528859	16095	118398
6/29/20	India	19459	380	548318	16475	123036
6/30/20	India	18522	418	566840	16893	126625
7/1/20	India	18653	507	585493	17400	129310
7/2/20	India	19148	434	604641	17834	131536
7/3/20	India	20903	379	625544	18213	135143
7/4/20	India	22771	442	648315	18655	139362
7/5/20	India	24850	613	673165	19268	144306
7/6/20	India	24248	425	697413	19693	149095
7/7/20	India	22252	467	719665	20160	152825
7/8/20	India	22752	482	742417	20642	156924
7/9/20	India	24879	487	767296	21129	162655
7/10/20	India	26506	475	793802	21604	168258

Variables Entered/Removed[b]

Model	Variables Entered	Variables Removed	Method
1	Total deaths[a]	.	Enter

a. All requested Variables entered.
b. Dependent Variable: new cases

Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.974a	.949	.947	1249.02414

a. Predictors: (Constant), total deaths

ANOVA[b]

Model		Sum of squares	df	Mean Square	F	Sig.
1	Regression	1.098E9	1	1.098E9	703.792	.000a
	Residual	59282329.761	38	1560061.309		
	Total	1.157E9	39			

a. Predictors: (Constant), total deaths
b. Dependent Variable: new cases

Coefficients[a]

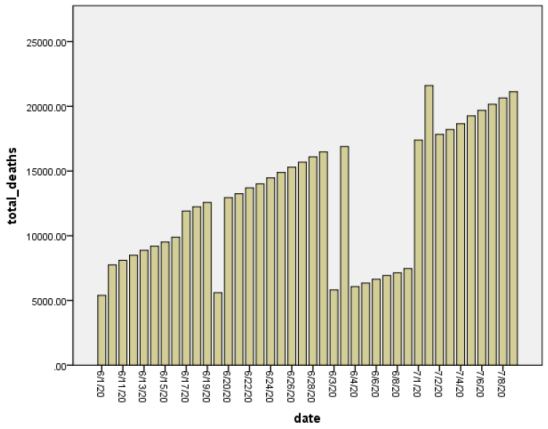
Model		Unstandardized coefficients		Standardized coefficients		
		B	Std. Error	Beta	*t*	Sig.
1	(Constant)	1934.551	540.829		3.577	.001
	total deaths	1.039	.039	.974	26.529	.000

a. Dependent Variable: new cases

Correlation

		New cases	new deaths	Total cases	Total deatha
New cases	Pearson Correlation	1	.148	.985	.974
	Sig. (2-tailed)		.363	.000	.000
	N	40	40	40	40
New deaths	Pearson Correlation	.148	1	.204	.248
	Sig. (2-tailed)	.363		.206	.123
		40	40	40	40
Total cases	Pearson Correeiation	.985	.204	1	.988
	Sig. (2-tailed)	.000	.206	40	.000
	N	40	40		40
Total deaths	Pearson Correeiation	.974	.248	.988	1
	Sig. (2-tailed	.000	.123	.000	40
	N	40	40	40	

**.Correlation is significant at the 0.01 level (2-talled)



Results

The above analysis reveals that COVID-19 Patients treating with repurposing Drugs survived and the mortality rate decreased.

Discussion

In this article design, strategies for some of the drugs effective against COVID-19 are represented also focusing through light on the listing of drugs that are currently testing under clinical trials for COVID-19 virus with their mechanism of action. Repurposing drugs may have some side effects associated with heterocycles and also potentiate the efficiency of the molecule.

Conclusion

Based on current knowledge concern COVID-19, drugs that combine anti-inflammatory and antiviral effects and have a favorable adverse effects profile, should be the most promising strategies to fight this viral infection. At the starting of pandemic time, repurposing drugs are used that those already tested on humans. The current situation highlights the urgency for clinical trials and vaccine development for clinical uses.

The non-therapeutic approaches as effective measures to control disease spread. These may include social distancing, using a mask, improving immunity, taking proteinaceous food, washing hands, and quarantine of suspects.

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The study has indeed helped me to explore more knowledgeable avenues related to my topic and I am sure it will help me in my future.

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